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The Benefits of Pulmonary Rehabilitation Program on Post-Tuberculosis Bronchiectasis

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Abstract

Pulmonary rehabilitation has emerged as a recommended standard of care for patients with chronic lung disease. As in chronic obstructive pulmonary disease (COPD), persons with other forms of chronic respiratory disease commonly experience deconditioning and decreased quality of life. The aim of this prospective study is to determine the effect of a 4-week pulmonary rehabilitation program (PRP) on patients diagnosed with post-pulmonary tuberculosis bronchiectasis in the Philippines. The participants were above 18 years of age, diagnosed to have stable Post-Pulmonary tuberculosis bronchiectasis with chest computerized tomography (CT) scan or chest radiograph showing bronchiectatic changes, consented to attend the PRP sessions and be included in the study. The subjects underwent PRP for 4 weeks with a total of 8 sessions and determination of Forced expiratory volume at 1 second (FEV1), forced vital capacity (FVC), quality of life determination using the Saint George Respiratory Disease Questionnaire (SGRQ), and exercise endurance using the 6-minute walking test (6 MWT), before and after the PRP. A total of fourteen patients, six males and eight females, aged from 28 - 72 years old, completed the 4-week pulmonary rehabilitation program. There were four ex-smokers and ten non-smokers with concomitant asthma and COPD in some patients. There was significant improvement in the 6-minute walk test and quality of life after 4 weeks of rehabilitation program among the subjects with p value for 6 MWT at $p = 0.0001$ and $p = 0.008$ for SGRQ. Conclusion: Pulmonary rehabilitation program led to a significant improvement in exercise capacity and health related quality of life among patients with post-pulmonary tuberculosis bronchiectasis.

Keywords

Pulmonary Rehabilitation, Post-Tuberculosis Bronchiectasis, Post-Tuberculous Lung Disease

1. Introduction

Bronchiectasis is a heterogeneous and chronic disorder of the major bronchi and bronchioles characterized by permanent abnormal dilatation and destruction of bronchial walls [1]. The induction of bronchiectasis is based on the vicious cycle concept wherein repeated infectious insults on the airways cause persistent inflammation, impairment of drainage of secretions, airway obstruction, and eventual destruction of these airways [2]. The classic clinical manifestations of bronchiectasis are cough and the daily production of mucopurulent and tenacious sputum lasting months to years [3]. Less specific complaints include dyspnea, hemoptysis, wheezing, and pleuritic chest pain [2].

Infectious etiologies for bronchiectasis are varied and a significant cause is tuberculosis (TB) [2]. Endobronchial tuberculosis commonly leads to bronchiectasis, either from bronchial stenosis or secondary traction from fibrosis [3]. The Philippines ranked fourth among all countries with the highest tuberculosis incidence in 2020 with 1 million Filipinos still having active tuberculosis [4]. Tuberculosis also ranks as the 12th leading cause of death in the country in 2020 and there is no data on the number of Filipinos suffering from post-TB sequelae [4]. Worldwide, The Union estimates a total of 155 million TB survivors alive in 2020 with, as much as 50% of these individuals, still complaining of residual cough, dyspnea, weakness and impairment in their physical capacity [5]. The Union, together with a global consensus of TB experts, labelled this constellation post-TB sequelae as Post-TB Lung Disease (PTLD) when there is "evidence of chronic respiratory abnormality, with or without symptoms attributable at least in part to previous pulmonary tuberculosis." [5].

Pulmonary rehabilitation has emerged as a recommended standard of care for patients with chronic lung disease based on a growing body of scientific evidence [6]. The primary goal is to restore the patient to the highest possible level of independent function. Pulmonary rehabilitation is an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities [7].

Rehabilitation programs for patients with chronic lung diseases are well-established as a means of enhancing standard therapy in order to control and alleviate symptoms and optimize functional capacity [6] [7] [8]. It has also been applied successfully to patients with other chronic lung conditions such as interstitial diseases, cystic fibrosis, bronchiectasis, and thoracic cage abnormalities [6]. Recent guidelines on the management of bronchiectasis likewise strongly recommend pulmonary rehabilitation intervention and regular exercise for adult patients with bronchiectasis and exercise capacity limitation with the goals of improving the patients' symptoms and physical capacity [2] [3].

On the other hand, studies on tuberculosis leading to bronchiectasis and the subsequent role of pulmonary rehabilitation in post-tuberculosis bronchiectasis are scanty and more data are needed, particularly from countries with high burden of pulmonary tuberculosis [9] [10] [11] [12] [13]. This scarcity of specific

evidence on PTLD and the benefits of pulmonary rehabilitation are acknowledged by The Union so that the First International Symposium on Post-TB disease was held to establish the "Clinical standards for the assessment, management and rehabilitation of post-TB lung disease" with 75 global TB experts comprising the consensus panel [14]. The aim of the implementation of these standards was to gather evidence while management and rehabilitation of PTLD may be performed in a rational, cost-effective and standardized manner [14].

This study aims to add to the needed data on PTLD and pulmonary rehabilitation intervention in PTLD by determining the effect of a 4-week pulmonary rehabilitation program on patients diagnosed with Post-Pulmonary tuberculosis Bronchiectasis based on Chest X-ray and/or CT scan as to spirometry, quality of life, and functional capacity, before and after the program.

2. Methods

2.1. Subjects

Fourteen patients, male and female, were enrolled in this prospective study and underwent the out-patient pulmonary rehabilitation program of the Philippine General Hospital in 2015. The subjects underwent an out-patient pulmonary rehabilitation program for 4 weeks, given 2 times a week with a total of 8 sessions. The subjects included were all above 18 years of age, diagnosed to have Post-pulmonary tuberculosis bronchiectasis, which have completed tuberculosis treatment, with chest CT Scan or chest radiograph showing bronchiectatic changes, consented to attend PRP sessions and join the study. Exclusion criteria were uncontrolled co-morbid illnesses limiting performance of measured parameters & significantly affecting quality of life such as: severe cardio-vascular disease, uncontrolled diabetes mellitus with or without end-organ damage, debilitating or uncontrolled malignancies, psychological or intellectual defects limiting comprehension, and physical defects limiting mobility or ambulation. None of the patients showed any evidence of ischemic heart disease, musculoskeletal disorders, or other disabling disorders that could limit participation in the rehabilitation program. All patients agreed to participate in the rehabilitation program and the study. This study was approved by the ethics review board of the institution.

2.2. Intervention

The pulmonary rehabilitation program was conducted twice weekly for 3 hours for 4 weeks with 2 - 4 participants in each session and supervised by a pulmonologist, physiotherapist, nutritionist and psychiatrist. The exercise program as mainly a symptom-limited walking-based protocol with 30 minutes each session to aim for a Borg's dyspnea score of 4 - 5 along with upper and lower limb resistance training. Breathing re-training & dyspnea-relieving techniques were also included in the sessions. Education interventions, nutrition and psychologic counselling, and occupational or activities of daily living adjustments were integral in

the program. A home exercise program and the use of a diary of activities and an action plan for exacerbations were emphasized.

2.3. Outcome Measurements

Resting Lung Function: Post-bronchodilator FEV1, FVC, and FEV1/FVC were measured before and after completion of the PRP with the best of three efforts selected for each parameter. The Microlab spirometer was used.

Exercise capacity as measured by the 6-Minute Walk Test: The distance the patient was able to walk in 6 minutes was determined in a measured corridor while the patient was instructed to walk at his fastest pace and longest possible distance under direct supervision of the investigator. This was performed before and after completion of PRP.

Dyspnea and Health Related Quality of Life: St. George's Respiratory Questionnaire is a self-administered Health Related Quality of Life measure containing 50 items and 76 weighted responses divided into the three domains of symptoms, activity, and impacts. SGRQ is a valid measure for bronchiectasis in that it can distinguish between different levels of impaired health and appears to be sensitive to spontaneous changes in health over a 6-month period [15] [16] [17]. The SGRQ was administered before and after undergoing the PRP.

2.4. Statistical Analysis

The relevant features of the patients were reported in percentages. The lung function test values were reported as percent of predicted for the normal Filipino population while the SGRQ scores and 6 MWT values were in their actual unit measures.

The paired t-test was utilized to evaluate the effect of PRP before and after its administration for the different outcome measures established in this study. A p value of <0.05 was considered to be significant.

3. Results

A total of fourteen patients, six males and eight females, age ranged from 28 - 72 years old, were included in the study (**Table 1**). Consent was given by all the patients. They all underwent the pulmonary rehabilitation program and completed eight sessions. There were four ex-smokers and ten non-smokers. Ninety-three percent of the patients had significant occupational exposure to dust or chemicals. Concomitant chronic respiratory illnesses were noted of which four had COPD and five had bronchial asthma. Sixty-four percent among the patients had an inhaled corticosteroid-containing treatment while 71% were given an inhaled bronchodilator. Twenty-eight percent of the patients were not on any form of inhaled medication.

Baseline means lung function of the patients showed a post-bronchodilator moderate degree of airflow obstruction that would qualify also these patients under the definition of COPD. The mean baseline 6 MWT test value of355.5 ± 94.9

Table 1. Baseline characteristics of the study subjects with Post-TB bronchiectasis.

Feature	No. of subjects (% from total of 14 subjects)
Gender:	
Male	6 (43%)
Female	8 (57%)
Age, range (years)	28 - 72 years
Previous smoking history	4 (28%)
COPD, doctor-diagnosed	4 (28.6%)
Asthma, doctor-diagnosed	1 (35.7%)
Current occupation:	
Mechanic, driver	2 (14.2%)
Beautician, domestic worker	2 (14.2%)
Factory worker	7 (50%)
Farmer	1 (7.14%)
Office worker	1 (7.14%)
None	1 (7.14%)
Number of patients currently on pharmacologic regimen:	
Inhaled corticosteroid-long-acting beta-2 agonist combination (ICS-LABA)	8 (57.1%)
Inhaled short-acting beta-2agonist-anti-muscarinic combination (SABA-SAMA)	1 (7.14%)
Combination ICS-LABA and LAMA	1 (7.14%)
None	4 (28.6%)

meters is lower than reference values utilized in other studies, reflecting an impairment of exercise capacity (Table 2). The baseline means SGRQ score of the patients was 39.0 ± 18.8 units which reflect a generally poor quality of life if the threshold 25 units and above is also adopted for bronchiectasis, similar to COPD [17]. All the domains of symptoms, activity and impacts ranked low for the patients in the study (Table 3).

Upon comparing the baseline and post rehabilitation values of the patients, there was a statistically significant improvement in the exercise capacity using the 6 MWT (p value = 0.0001) and in the quality of life of the patients, based on the SGRQ score (p value = 0.008) (Table 2 and Table 3 and Figure 1). The mean improvement of 114.6 meters in the 6 MWT after the 4 weeks of PRP is a substantial improvement above the minimal clinically important difference (MCID)

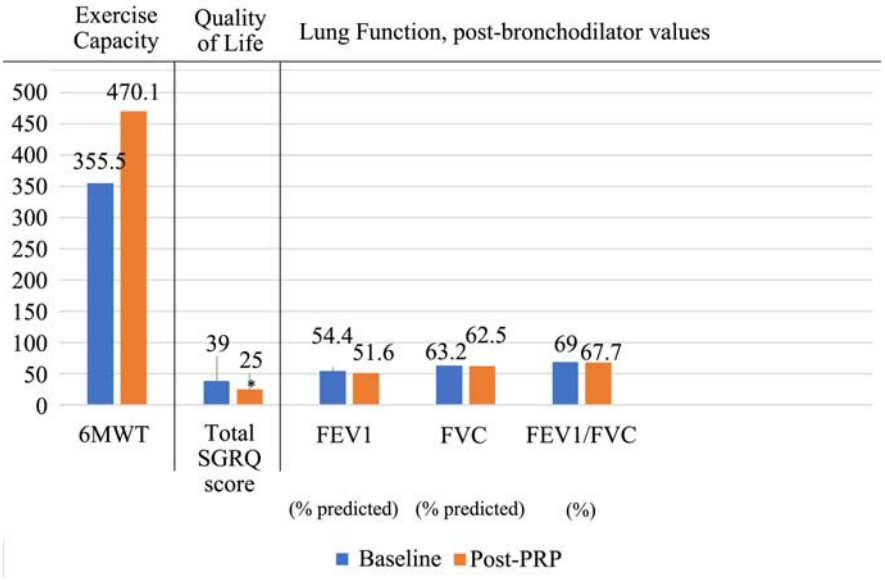

Figure 1. Summary of outcome parameters of study subjects before and after 4-week pulmonary rehabilitation, (n = 14 post-TB Bronchiectasis patients). *p < 0.05: statistically significant difference and above minimal clinically important difference. 6 MWT: 6-minute walk test; SGRQ: St. George Respiratory Disease Questionnaire; FEV1: Forced expiratory volume at 1 second; FVC: Forced vital capacity.

Table 2. Lung function test post-bronchodilator and exercise capacity results of study patients at baseline and after a 4-week Pulmonary Rehabilitation Program (PRP), (n = 14 post-TB Bronchiectasis patients).

Lung Function Test & Exercise Capacity Parameter	Mean	Standard deviation	Median	Range	p-value
FEV1 (% predicted)					**0.14**
Baseline	54.4	24.0	51.0	22 - 91	
Post-PRP	51.6	21.9	51.5	22 - 91	
FVC (% predicted)					**0.64**
Baseline	63.2	19.7	60	28 - 95	
Post-PRP	62.5	18.4	62.5	27 - 90	
FEV1/FVC (post-bronchodilator %)					**0.50**
Baseline	69.0	15.2	68.5	42 - 88	
Post-PRP	67.7	15.3	72.0	41 - 88	
Exercise Capacity by the 6 MWT 6 MWT (meters)					**0.0001***
Baseline	355.5	94.9	358.5	147.6 - 482.5	
Post-PRP	470.1	76.9	462.3	348.9 - 645.3	

*p value < 0.05 is considered as statistically significant. FEV1: Forced expiratory volume at 1 second; FVC: Forced vital capacity; 6 MWT: 6-Minute walk test.

Table 3. Quality of life or the St. George's Respiratory Questionnaire (SGRQ) Scores of study subjects at baseline and after 4 weeks of pulmonary rehabilitation program, (n = 14 post-TB Bronchiectasis patients).

Quality of Life based on SGRQ Score	SGRQ Scores, unit Mean (Standard Deviation)		p-value
	Baseline	Post-rehab	
Domain: Symptoms	40.7 (25.9)	26.6 (21.7)	0.04*
Domain: Activity	46.7 (16.4)	36.9 (19.9)	0.03*
Domain: Impact	34.1 (22.4)	17.8 (10.7)	0.007*
Total Score	39.0 (18.8)	25.0 (12.6)	0.008*

*p value < 0.05 is considered as statistically significant. SGRQ: Saint George Respiratory Disease Questionnaire.

of 70 meters established for patients with chronic lung diseases [18]. The decrease in the SGRQ score among the subjects by 14 units after PRP is also above the MCID of 4 units identified for patients with chronic lung diseases [19]. This significant improvement in quality of life was consistent among the three domains of symptoms, activity and impacts.

After 4 weeks of the PRP, the lung function of the patients did not significantly change based on the FEV1 (p = 0.14), FVC (p = 0.64), and FEV1/FVC (p = 0.50) values (**Table 2** and **Figure 1**).

4. Discussion

This study in a low-to-middle-income country with a high burden of tuberculosis, such as the Philippines, shows similar efficacy of pulmonary rehabilitation as other studies among patients with post-tuberculosis bronchiectasis in improving their exercise capacity and quality life [9] [10] [11] [12] [13]. This improvement is well above the established minimal clinically important difference levels [18] [19]. It is notable that all the subjects manifested with a persistently significant airflow obstruction which would place them under the diagnosis of COPD. These patients were also pharmacologically treated by their physicians as having chronic airflow obstruction. This highlights the heterogeneity and overlap of the different pathologies present in post-tuberculosis lung disease (PTLD) that is still currently being investigated as a distinct clinical syndrome [20]. Allwood et al emphasize that the host-pathogen interaction is extremely complex with the extent of eventual lung damage reliant on the processes of granuloma formation and recovery, the interplay of the T and B lymphocytes, cytokines, tumor necrosis factor alpha, interleukins and matrix metalloproteinases and the genetic predisposition to incur such lung pathologic sequelae [20]. Tuberculosis as a risk factor for the development of COPD is acknowledged and this was similarly observed in the Philippine Burden of Lung Disease (BOLD) study with the history of TB increasing the odds ratio of having the diagnosis of COPD at 6.31 (95% confidence interval 2.67% - 15.0%) [21].

In the study of Jones *et al.*, they utilized the additional screening criterion of MRC (Medical Research Council) dyspnea scale 2 or above that would indicate significant dyspnea prior to enrolling the patients with post-TB bronchiectasis for pulmonary rehabilitation [11]. This current study did not limit its enrollment to the PRP to symptomatic patients although the mean symptom SGRQ score of the subject population indicates high symptomatology.

Pulmonary rehabilitation benefits patients with bronchiectasis by improving their exercise capacity though the increase in aerobic capacity of peripheral muscles, improved disease management and quality of life [2] [3]. These mechanisms probably were operational in the improvement seen in this study's subject population. The PRP was shorter and utilized simple interventions that can readily be performed in resource-limited settings but, nevertheless, resulted to the improvement in the pre-determined patient-related outcomes.

The synergy of pharmacologic management of airflow obstruction and non-pharmacologic PRP to improve the exercise capacity and quality of life of COPD patients should similarly be adopted in the management of PTLD [8]. The patients in this study all showed chronic airflow obstruction which majority of the attending physicians recognized and managed pharmacologically as well.

Lung function test values have not been shown to improve with PRP among patients with COPD and bronchiectasis and are not the appropriate outcomes targeted for treatment with PRP [2] [3]. Similarly, the studies on PRP among post-TB bronchiectasis also did not show improvement in lung function test values as also observed in this study.

The standards of care for rehabilitation of PTLD patients established by the consensus panel of The Union's First Symposium are timely in setting the bar for adequate PRP interventions [14]. These standards also provide a unified approach and common language in managing this newly identified and complex syndrome of PTLD. Study results will be easier to interpret with the common standards and identified outcome indicators.

This study had several limitations with a small number of subjects and exacerbations not being accounted for. Severity of bronchiectasis was also not determined. A randomized trial on PRP in PTLD is urgently needed.

5. Conclusion

Pulmonary rehabilitation program led to a significant improvement in exercise capacity and health-related quality of life among patients with post-tuberculosis bronchiectasis when compared to baseline in a low-to-middle-income country setting. Larger and randomized studies are needed to firmly establish the role of pulmonary rehabilitation not only for post-tuberculosis bronchiectasis but for the large number of patients affected by post-tuberculosis lung disease (PTLD) as well.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Probiotics for Antibiotic-Associated Diarrhea: What, When, and How Long?

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Abstract

Probiotics have been formally defined as "live microorganisms that confer a health benefit on the host when administered in adequate amounts." Although a range of applications has been explored for probiotics, their utility in antibiotic-associated diarrhea (AAD) is both biologically plausible and supported by abundant clinical evidence. However, the strength of evidence underlying the efficacy of specific strains and formulations for AAD varies widely. This review leverages recent meta-analyses and systematic reviews to clarify some outstanding issues on the utility of probiotics for AAD, including which strains have evidence for efficacy in AAD, what doses have been demonstrated to be effective, and the optimal duration of probiotic therapy, and provides practical guidance on how to select an appropriate product. Some trends emerged in this analysis of recent meta-analyses and systematic reviews, including: 1) Certain probiotics, such as *Saccharomyces boulardii* and some *Lactobacilli*-containing products, are consistently found to be effective for the management of AAD; 2) Dosing thresholds for efficacy exist that must be achieved through the administration of probiotics that reliably contain the labeled amounts of probiotic constituents; 3) Most effective probiotics are initiated at the same time as antibiotic therapy and continued for between 1 and 3 weeks after the cessation of therapy. These data suggest that attention must be paid to species, dose, and duration when selecting an appropriate product for patients initiating antibiotic therapy; further considerations may include the antibiotic used and the patient's baseline risk for AAD.

Keywords

Probiotics, AAD, *Saccharomyces boulardii*, *Lactobacilli*

1. Introduction

The human microbiome is a community of microorganisms that can be found

nearly everywhere in the body but is particularly dense and complex in the luminal spaces of the gastrointestinal (GI) tract [1]. The most recent estimates suggest that a person of average size and weight contains 30 trillion human cells and 39 trillion bacteria—a greater than 1 to 1 ratio of human cells to microbes [2]. It is thus unsurprising that this community can have profound direct and indirect effects on human health.

The mechanisms by which the human microbiota exert these effects have been under intensive study for at least the last 5 decades; however, the first recorded use was in ancient China, where human feces were used to manage gastrointestinal complaints [3]. It was not until the early twentieth century that Elie Metchnikoff, a physician working at the Pasteur Institute, directly linked the consumption of certain fermented dairy products to human health [4]. The discovery of *Saccharomyces boulardii* in 1920 was a pivotal moment in probiotic history, marking the first time that supplementation with a specific species of microorganism was directly linked to protection against GI disease—in this case, diarrhea occurring as the result of a widespread cholera outbreak in Southeast Asia [5].

Today, probiotics have become an important part of self-care regimens for many people, with one recent (2021) survey of more than 13,000 consumers finding that nearly one-quarter had deliberately used a probiotic-containing product in the previous 6 months [6]. Probiotics have also become widely used in clinical practice, particularly for the management of GI disorders, as highlighted by recent guidelines published by the American Gastroenterological Association (AGA) [7]. They are widely available in various single- and multiple-organism products administered orally in a manner analogous to conventional pharmaceuticals or in combination with a variety of foods.

The World Health Organization defines probiotics as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [8]. Probiotics have been more precisely defined by the International Scientific Association for Probiotics and Prebiotics (ISAPP) as "live microorganisms with a suitable viable count of well-defined strains with a reasonable expectation of delivering benefits for the wellbeing of the host" [9]. Unfortunately, the marketplace has hundreds or even thousands of products labeled as "probiotics" but that do not meet even these minimal criteria. Furthermore, claims have proliferated for these agents, and they have been marketed both for biologically and clinically plausible uses, such as for antibiotic-associated diarrhea (AAD), as well as for disease states in which their use is supported by limited and contradictory evidence at best. The lack of strong evidence for their use in most GI conditions has been highlighted by the AGA guidelines, which give "conditional" recommendations, or no recommendation at all, for their use in many disease states [7].

AAD is well recognized to be associated with increased morbidity and mortality, prolonged hospital admissions, and a high cost of care [10] [11] [12] [13]; further, it is also an important reason for premature antibiotic discontinuation

[14]. Thus, readily accessible adjunctive therapies that can reduce the risk for AAD or limit its duration are highly desirable. In contrast to the limited evidence available for the efficacy of probiotics in other disease states, a broad consensus has emerged that these products may be effective in the prevention of AAD in general and/or *Clostridioides difficile*-associated diarrhea (CDAD) specifically, leading to guideline recommendations of varying strengths in this setting [7] [15] [16].

The strength of the evidence for specific probiotic strains and formulations for AAD varies widely, and there are still gaps in knowledge. Perhaps more than any other product used routinely to affect human health, probiotics cannot be considered a homogeneous class, and the potential clinical benefits and risks of these products probably vary by strain and dose [7]. Thus, if a therapeutic effect is desired, considerable care must be taken to select products with a clearly defined composition, appropriate viable counts, and evidence for health benefits. Guidelines recognize this heterogeneity by recommending only specific probiotic formulations [7] [16]. Although less well addressed in guidelines, it would be expected that—like any product with a clinical effect—it is critical to administer these agents at doses and for durations that are most likely to have a therapeutic benefit. This paper seeks to fill some of the knowledge gaps.

Here, we focus on the utility of probiotics in AAD to clarify some outstanding issues regarding their use for this indication. Given their inherent low risk for adverse events (AEs); the consistent, albeit moderate-quality, evidence for the benefits of probiotics in the prevention of AAD; and their low cost (relative to the cost of managing AAD), we attempt to address whether carefully selected probiotics, administered in doses and durations according to best available evidence, should be a routine part of care in patients who are prescribed antibiotics.

2. Antibiotic-Induced Alterations in the Gut Microbiota

Antibiotics are well-known to perturb the normal GI microbiota, opening niches where pathogenic bacteria can thrive and resulting in diarrhea [17]. Antibiotics are likely not a homogeneous class in terms of their effects on the microbiota, and the risk for AAD may vary by mechanism of action, spectrum of activity, duration of treatment, and other factors [18]. Thus, it is difficult to draw any firm conclusions on the effect of an individual antibiotic on the composition of the microbiome.

One meta-analysis of studies evaluating common antibiotics for upper respiratory and urinary tract infections found that all antibiotics suppressed bacterial diversity and resulted in substantial shifts in the microbiota composition [19]. However, generalization of the effect of antibiotics was hampered by methodologic inconsistencies and a failure to consistently define normal baseline microbiota composition. A second systematic review of 129 studies also found widely disparate effects of antibiotics on the gastrointestinal microbiota, including impacts on species and taxa that would be expected to be associated with an increased risk for AAD [18]. Some studies have reported the time for the gut mi-

crobiota to recover to baseline; in these studies, the time to restoration to baseline ranged from 6 to 8 weeks after stopping aminoglycosides to between 1 and 4 years after ciprofloxacin, clindamycin, and clarithromycin in combination with metronidazole [18].

It is clear most antibiotics have significant, albeit disparate, effects on the gut microbiome. These differential effects on the microbiome may translate to different risks for AAD. Clinically, data from a study conducted in hospitalized patients suggest that β-lactams are associated with substantially higher rates of GI AEs (defined in this study as the composite of nausea, emesis, and non-*C. difficile* diarrhea; 17.4/10,000 person-days) as compared with non–β-lactams (ranging from no GI AEs to 12.4/10,000 person-days) [20]. Although most β-lactams in this analysis were associated with relatively high rates of AAD, some, such as oxacillin, were associated with rates above 30/10,000 patient-days. Of the non–β-lactams, only doxycycline (12.4/10,000 person-days) and trimethoprim-sulfasalazine (11.2/10,000 person-days) approached the rates seen with most β-lactams. The rates reported in this study are probably substantial underestimates of the true incidence of AAD by class, as the underlying data were derived from a hospital with an active antibiotic stewardship program that likely had a strong influence on both the use and duration of antibiotic treatment, with a resulting reduction in the overall incidence of AAD. It is important to emphasize that because these data reflect only hospitalized patients, they may not reflect the incidence of diarrhea in the outpatient population, which may often go unreported.

Although evidence is limited on which to base firm recommendations, it is possible that patients treated with certain antibiotic classes, such as β-lactams, may benefit most from proactive use of probiotics to prevent diarrhea, with initiation at the same time as antibiotic therapy and continuation for at least several weeks thereafter. This strategy is also supported clinically by the meta-analyses discussed below. While the methodologic issues with attempting to synthesize these data limit interpretation, both the microbiologic and clinical data point toward differential effects of antibiotics on gut microbiota. All antibiotics likely cause at least some degree of microbial perturbation (dysbiosis) that lasts weeks to years after cessation of antibiotic treatment. Among patients treated with antibiotics known to result in extended disruption of the GI microbiome, more prolonged administration periods following antibiotic cessation are at least biologically plausible, although there is no strong clinical evidence for or against this strategy.

3. How Do Probiotics Treat AAD?

Selected probiotics have consistently shown efficacy in AAD. However, the mechanisms by which they exert these activities remain under active investigation and are in some cases unclear [3] [17] [21] [22]. Again, it is important to emphasize that probiotics are highly heterogeneous, and the effects of one probiotic on various parameters do not necessarily indicate that other probiotics will have the same effects.

Until recently, it was thought that probiotics do not colonize the GI tract. However, recent evidence suggests that some may become long-term residents of the GI tract—at least in some people and under some conditions. One recent study evaluated whether twice-daily administration of bacterial probiotic to healthy volunteers was associated with colonization or changes in host microbiota function [23] [24]. In this study, some probiotic strains persistently colonized the GI mucosa; however, inter-individual differences were detected. Approximately half of the participants were "permissive" to colonization, and in these patients, probiotic strains were detectable at 3 weeks post-administration. The other half were "resistant" and showed no sign of colonization. In a second study using the same probiotic strains, 1 week of ciprofloxacin and metronidazole was administered to healthy subjects to eliminate their microbiome; these subjects were divided into a control group, a fecal transplant group, and a group that received 4 weeks of treatment with the study probiotic. Among those who received probiotics, there was clear evidence for colonization by probiotic strains and reconstitution of the baseline microbiota was delayed [25]. This finding is consistent with the hypothesis that destruction of the native microbiome opens niches that probiotic strains can occupy, potentially augmenting the community of commensal bacteria that existed prior to antibiotic treatment and resulting in a long-term shift in gut microbe composition [23]. This replacement, whether temporary or long-term, may contribute to the reduction in risk for post-anti-biotic diarrhea seen with some probiotic products.

Aside from their potential ability to colonize and replace commensal bacteria destroyed by antibiotic treatment, several other mechanisms have been advanced for the effects of probiotics in AAD. Some of the more plausible effects are summarized in **Table 1**, although it should be cautioned that this is not a comprehensive review of postulated probiotic mechanisms of action, which have been discussed in detail elsewhere [26].

4. Probiotics for AAD

A broad range of single- and mixed-species probiotics are currently marketed for an equally broad array of health claims. As outlined earlier, it is clear probiotics should not be considered a homogeneous class. Indeed, for every product with evidence for efficacy in AAD, there are many more with little, if any, supporting data. Probiotics that have most often been the subject of study in appropriately designed clinical trials include single species or mixtures of *Saccharomyces boulardii*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Bifidobacteria bifidum*, *Bifidobacteria longum*, *Streptococcus thermophilus*, and *Clostridium butyricum* [27]. However, many other species and mixtures also have been evaluated.

Given the heterogeneity in study designs and patient populations, it is challenging to derive precise guidance on the selection and clinical use of probiotics from individual studies. However, there are some consistencies across studies

Table 1. Selected mechanisms of action of probiotics in AAD.

Competitive exclusion	May outcompete pathogenic bacteria by consuming nutritional resources, producing antibacterial molecules, or modulating the pH of the gastrointestinal macroenvironment. [26]
Effects on intestinal SCFAs	May maintain SCFA (acetate, propionate, and butyrate) concentrations during antibiotic use, reducing diarrhea by promoting sodium and water absorption. [21]
Effects on bile acid concentrations	Some probiotic strains may attenuate antibiotic-induced increases in colonic primary bile acids that may increase susceptibility to *Clostridioides difficile* infection. [21] [36]
Effects on barrier function	May prevent antibiotic-induced disruption in the intestinal barrier. [21] [37]
Immune effects	May reduce antibiotic activation of inflammatory pathways. [21] [26] *Lactobacillus* and *Saccharomyces*-based probiotics may upregulate the innate and adaptive immune systems. [28]

AAD = Antibiotic-Associated Diarrhea; SCFA = Short-Chain Fatty Acid.

that meta-analyses and systematic reviews have uncovered. These data can guide treatment choice, dose, and duration of therapy in the absence of large-scale, randomized, placebo-controlled studies.

4.1. What Is the Efficacy of Probiotics for AAD?

The efficacy of probiotics has been evaluated in several recent meta-analyses and systematic reviews for CDAD specifically and for the broader category of AAD regardless of causative organism [27] [28] [29]. These analyses consistently show that certain probiotics are effective in diarrhea prevention, with the effect often being driven by patient subgroups at higher baseline risk for these events.

A meta-analysis conducted by Goldenberg and colleagues explored the efficacy of probiotics in CDAD [29]. The analysis included 39 studies overall (9955 participants); among the 31 adequately conducted trials, probiotics were associated with a 60% reduction in risk for CDAD (1.5% with probiotics vs 4.0% with placebo or no treatment; risk ratio [RR] 0.40; 95% CI, 0.30 - 0.52). Per the results of a post-hoc analysis, probiotics were only effective in reducing risk for CDAD in high-risk patients. The authors noted that probiotic prophylaxis would prevent 85 CDAD episodes per 1000 patients at high risk for CDAD.

These data suggest that probiotics have a large protective effect against CDAD that is particularly evident in patients who are at high baseline risk for the disease; however, this species—despite being the single most commonly isolated organism in AAD—accounts for no more than 20% of all AAD cases [30]. A

second meta-analysis conducted by Goodman and colleagues sheds light on the efficacy of probiotics for AAD regardless of the causative organism. This analysis included 42 randomized, controlled studies of adults (N = 11,305) who received either a probiotic or a control or no treatment [28]. The outcome was the incidence of AAD. Overall, coadministration of probiotics with antibiotics was associated with a 37% reduction in the risk for AAD (RR 0.63; 95% CI, 0.54 - 0.73; $P < 0.00001$), although this effect was driven mainly by reductions in subjects at moderate to high baseline risk for AAD.

A third meta-analysis, conducted by Guo and colleagues examined the utility of probiotics for pediatric AAD prevention [27]. A total of 33 randomized, parallel, controlled pediatric trials were included (N = 6352) that compared probiotics with placebo, active alternative prophylaxis, or no treatment. Probiotics evaluated in these studies included single species or combinations of *Bacillus* spp., *Bifidobacterium* spp., *C. butyricum*, *Lactobacilli* spp., *Lactococcus* spp., *Leuconostoc cremoris*, *Saccharomyces* spp., or *Streptococcus* spp. Across all studies, AAD occurred in 8% of the probiotic group and 19% of the control group, corresponding to a 55% reduction in the risk for AAD (RR 0.45; 95% CI, 0.36 - 0.56). After accounting for patients who were lost to follow-up, the incidence of AAD was 12% in the probiotic group vs 19% for the control group (RR 0.61; 95% CI, 0.49 - 0.77; $P < 0.00001$). Among patients who developed diarrhea, probiotics were associated with a reduction in duration of 0.91 days (MD −0.91%; 95% CI, −1.38 to −0.44), although only 8 studies reported this outcome and thus, the evidence was considered low certainty.

The efficacy of probiotics does not appear to be compromised by an increased risk for AEs. Current meta-analyses consistently report few AEs, a similar risk for AEs to controls, or a reduction in AEs in the probiotics group relative to the control group, [27] [28] [29] although serious AEs have been observed in immunocompromised or severely debilitated patients [27].

4.2. Which Strains Are Effective?

The acute and chronic response of the microbiome to probiotics, and thus their impact on disease, will vary not only by product but also on an individual basis depending on the pre-existing composition of the microbiota, antibiotics used, and individual host factors [24] [25]. However, only some probiotics have consistently demonstrated efficacy in reducing AAD. Across recent meta-analyses, systematic reviews, and guidelines, *S. boulardii* was consistently identified as an effective probiotic, regardless of the population studied (adult or pediatric CDAD and adult or pediatric AAD) (**Table 2**) [7] [27] [28] [29] [31]. Probiotics containing *L. acidophilus*, often in combination with *L. casei*, were also frequently included among those probiotics considered effective for these indications.

4.3. What Dose Is Effective?

By definition, probiotics must be given in adequate amounts to achieve a health

Table 2. Effective probiotics according to recent meta-analyses, systematic reviews, and guidelines (Goldenberg 2017, Goodman 2021, Guo 2019, Sniffen 2017, Su 2020).

	Patient Population	Effective Probiotics	
		Yeast	Bacteria
Meta-analyses			
Goldenberg *et al.* 2017 [29]	Prevention of pediatric CDAD	• *S. boulardii*	• *L. acidophilus plus L. casei*
Goodman *et al.* 2021[a] [28]	Prevention of adult AAD	• *S. boulardii*	• *L. acidophilus* • *L. bulgaricus* • *L. casei* • *L. paracasei* • *L. rhamnosus* • *Lactobacillus* spp. • *B. animalis* ssp. *Lactis* • *B. longum* • *B. licheniformis* • *B. subtilis* • *Bac. clausii*
Guo *et al.* 2019 [27]	Prevention of pediatric AAD	• *S. boulardii*	• *L. rhamnosus*
Systematic Review			
Sniffen *et al.* 2018 [31]	Prevention of AAD	• *S. boulardii*	• *L. casei* DN114001 • 3-strain combination: *L. acidophilus* CL1285, *L. casei* LBC80R, and *L. rhamnosus* CLR2
AGA Guideline			
Su 2020[b] [7]	Prevention of CDAD	• *S. boulardii*	• 2-strain combination: *L. acidophilus* CL1285 and *L. casei* LBC80R • 3-strain combination: *L. acidophilus*, *L. delbrueckii subsp bulgaricus*, *and B. bifidum* • 4-strain combination*: L. acidophilus*, *L. delbrueckii subsp bulgaricus*, *B. bifidum*, and *Strep. salivarius subsp thermophilus*

[a]Most studies in this analysis used probiotic formulations containing ≥ 1 probiotic species; a subgroup analysis was performed on all individual species mentioned in included studies. [b]Conditional recommendation; low-quality evidence: "patients who place a high value on the potential harms (particularly those with severe illnesses) or a high value associated on avoiding the associated cost and a low value on the small risk of *C. difficile* development (particularly in the outpatient setting) would reasonably select no probiotics." AAD = antibiotic-associated diarrhea; AGA = American Gastroenterological Association; *Bac.* = *Bacillus*; *B.* = *Bifidobacterium*; CDAD = *Clostridioides difficile*-associated diarrhea; *L.* = *Lactobacillus*; *S.* = *Saccharomyces*; *Strep.* = streptococcus.

benefit [8]. A universal "best dose" of these agents is difficult, if not impossible, to identify because of the inherent heterogeneity among products. Furthermore, it remains to be determined if there is a stringent dose-response relationship with probiotics; given that these are living organisms, it is unlikely that this relationship is as simple as it is for many conventional pharmaceutical products.

In some cases, the best doses of specific probiotics, such as the yeast *S. boulardii*, have been well defined through decades of clinical experience and clinical studies. Yeast-based probiotics are dosed in milligrams and the effective dose of

S. boulardii is typically 500 to 1000 mg/day. Evidence from meta-analyses can be used to guide effective dosing of some bacterially based probiotics. Although the data cannot be reliably generalized, there appears to be a threshold of approximately 5×10^9 CFU/day across many of the studies described here, above which efficacy is more often observed for bacterially based probiotics. In a subgroup analysis of the Goodman meta-analysis described earlier, dosages of 5×10^9 CFU/day were associated with a significant 46% reduction in the relative risk for AAD in 4 studies with adequate data (RR 0.54; 95% CI, 0.38 - 0.76; $P < 0.01$) [28]. The Guo pediatric meta-analysis found that high-dose ($\geq 5 \times 10^9$ CFU/day) probiotics were generally more effective than lower doses ($P = 0.01$) [27]. In this analysis, AAD occurred at a rate of 8% in the high-dose probiotic group vs 23% in the control group (RR 0.37; 95% CI, 0.30 - 0.46; $P = 0.00001$), whereas in the low-dose studies, the corresponding values were 8% and 13%, respectively (95% CI, 0.46 - 1.01; $P = 0.02$). The Sniffen systematic review identified a somewhat higher threshold of 10^{11} CFU/day for efficacy in AAD and a systematic review conducted by Ouwehand *et al.* found that doses above 10^{10} CFU/day were effective in this setting [31] [32].

4.4. How Long Should Probiotics Be Administered?

Given their broad use as preventive treatments in the setting of AAD, surprisingly few data are available on the appropriate duration of therapy in patients receiving antibiotics. In the Goodman meta-analysis, probiotics were administered for 5 days to 56 days; most probiotics were initiated concomitantly with antibiotics and continued for an additional week after completion of the antibiotic course [28]. In the Sniffen systematic review, most effective probiotics were started within a few days of antibiotic initiation and continued until 7 to 28 days following completion of the antibiotic course [31].

Studies of the long-term impact of antibiotics suggest that longer durations may be appropriate to provide adequate support during the period of time when the gut microbiota is compromised by antibiotic therapy and to facilitate a return to a stable state that may—or may not—reflect the baseline composition of the microbiota but that nevertheless is not associated with diarrhea. Facilitating rapid restoration of the gut microbiota to a stable, healthy state is desirable to close niches created by antibiotic therapy that may be filled by microbiota that are associated with a reduced benefit to the host [33] [34] [35].

4.5. Importance of Appropriate Probiotic Selection

Unlike the situation that pertains with FDA-approved branded conventional pharmaceuticals and their Orange Book-listed generic equivalents, it is critical to consider brand when selecting probiotics. Regardless of the probiotic chosen, quality control, manufacturing processes, stability over time, and formulation all play into the choice of an effective probiotic. Given that the probiotic market is largely unregulated, selection of probiotics from established manufacturers may be important. These products are more likely to be consistent from batch to batch, less

likely to include unlabeled strains/species, and are generally more likely to produce clinical results consistent with clinical data [31]. The label should adhere to certain minimum requirements; in addition to displaying the US Food and Drug Administration disclaimer, it should provide clear daily dose information, list the probiotic strains clearly, and not include unproven health claims [31].

5. Conclusions

As outlined here, recent meta-analyses consistently support the efficacy of probiotics for the prevention of AAD. However, there are wide disparities in the evidence underlying the efficacy of individual probiotics. Current meta-analyses, systematic reviews, and guidelines have consistently found that single-species *S. boulardii* probiotics are effective; certain *Lactobacilli* species are likely also effective for this indication, although the interpretation of these data is hampered by the fact that many of these probiotics are available only as complex mixtures.

The dosing and duration of therapy are as important as selecting products supported by evidence. Choosing a product that is likely to deliver the labeled dose of probiotics is critical. While few data are available to support the duration of therapy, the kinetics of microbiome recovery after antibiotic therapy suggest that it is reasonable to provide probiotic support for at least 1 to several weeks after antibiotic discontinuation.

Linking a specific probiotic product directly to the clinical evidence supporting its use can be challenging and more prospective studies are needed. On balance, recent meta-analyses, systematic reviews, and clinical guidelines provide adequate data to support the use of specific products for the prevention and management of diarrhea and it is important to emphasize that these results cannot be extrapolated to all products that call themselves "probiotics". Instead, it is critical to select products that are supported by existing evidence. It is also critical to understand that the efficacy of these products is highly dependent on quality control in manufacturing, thus it is important to select probiotics from trusted suppliers that meet FDA requirements for labeling.

Disclosures

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Endovascular Management of Vertebral Artery Aneurysms

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Abstract

Background: The management outcome of a series of ruptured vertebral artery (VA) aneurysms was reviewed. **Method:** This is a retrospective study of prospectively collected data of 60 cases with ruptured VA aneurysms in the author's database from the year 2004. All cases were managed with coiling, stent-assisted coiling, flow diversion or endovascular parent artery sacrifice. Nimodipine and hypertensive, hypervolemic therapy was applied as standard. Outcome was assessed at 6 months with modified Rankin score (mRS). **Results:** There were 26 females and 34 males. Age range is 18 to 70 with a mean age of 42. There were 27 dissecting aneurysms and 33 saccular aneurysms. 50 (83%) cases were World Federation of Neurological Surgeons (WFNS) grade one to three. There were four WFNS grade four and six WFNS grade five. 25 cases of dissecting aneurysms were managed with parent artery coil occlusion. Two dissecting aneurysms affecting the dominant VA were treated with flow diverters. At 6 months follow up 50 (83%) achieved good outcome with mRS one to two. There were eight cases with poor outcome and two deaths. Six-month follow-up MR angiogram documented stable occlusion for the 24 cases with dissecting aneurysms treated with parent artery coil occlusion who survived. The two treated with flow diversion demonstrated good remodelling at 6 months on angiography. Six-month follow-up angiogram for the 32 cases of saccular aneurysm who survived documented stable aneurysm obliteration. **Conclusion:** Good outcome can be achieved with endovascular treatment for ruptured VA aneurysms. Parent artery occlusion is a safe and effective technique for ruptured VA dissecting aneurysm.

Keywords

Vertebral Artery, Aneurysm, Dissecting Aneurysm, Dissection

1. Introduction

VA aneurysm accounts for 0.5% to 3% of intracranial aneurysms [1]. In the In-

ternational Subarachnoid Aneurysm Trial (ISAT) VA aneurysms accounted for 1.4% of cases with subarachnoid hemorrhage [2]. The results of the ISAT study led to widespread adoption of endovascular treatment for ruptured aneurysms. The V4 intradural segment of the VA meets its contralateral counterpart to form basilar artery. The dominance of affected VA and its two important branches posterior-inferior-cerebellar artery (PICA) and anterior spinal artery (ASA) are the main determinants of strategies for treating ruptured VA aneurysm, surgically or endovascularly.

2. Methods

This is a retrospective study of a prospectively maintained database of cases with subarachnoid hemorrhage and aneurysms. The database was maintained with patients' consent for the purpose of audit and research publications without compromising patients' particulars. The inclusion criteria for this study were subarachnoid hemorrhage confirmed by lumbar puncture, documented on CT or MRI and catheter angiogram confirmed location of aneurysm along V4 segment of the VA up to vertebral confluence. Unruptured aneurysm and surgically managed cases including PICA-PICA bypass cases were excluded.

3. Results

A total of 60 cases met the criteria. There were 26 females and 34 males. Age range is 18 to 70 with a mean age of 42. 50 cases (83%) were WFNS grade one to three at presentation. There were four WFNS grade four and six WFNS grade 5. All cases with Glasgow Coma Scale of eight or less at presentation were intubated for airway control. Nimodipine, hypertensive, hypervolemic therapy were administered as standard. Intervention was performed either on the same day of admission or the next day.

Out of the 60 aneurysms, 27 had angiography findings of fusiform/nonsaccular dilatation of vertebral artery with proximal stenosis and "pearl and string sign". Although none of the cases showed pathognomonic double lumen or intimal flap, they were managed as dissecting aneurysms. 25 of the 27 cases involved co-dominant or non-dominant vertebral artery. They were managed with coil occlusion of the involved VA, taking care to preserve the PICA and ASA. For the coil occlusion procedure, no antiplatelet or anticoagulants were administered as these were cases with hemorrhage and there was a possibility that CSF diversion procedure may be required. The two cases involving dominant VA were treated with flow diverter insertion. For these two cases, intravenous integrilin and heparin were administered prior to flow diverter deployment. Subsequently the cases were maintained on aspirin and clopidogrel. At 6 months follow-up, among 22 cases who presented with good WFNS grade, 20 (91%) had good outcome and two (9%) had poor outcome. All 5 cases who presented with poor WFNS grade had poor outcome including one death. Overall, good outcome occurred in 20 out of 27 cases (74%), poor outcome occurred in 5 cases (19%)

including one death (4%) in this group of VA dissecting aneurysms.

Out of the 33 saccular aneurysms, two were giant aneurysms over 25 mm, two were large aneurysms over 10 mm and the rest were small aneurysms below 10 mm. Out of the 29 small aneurysms, only two had wide neck greater than 4 mm. The rest had favorable configuration of narrow neck aneurysms. The two giant aneurysms involved two young adults presenting with WFNS grade 5. One involved the non-dominant VA and the other involved the co-dominant VA. These two cases were treated with coil occlusion of parent VA successfully. Both cases had good recovery at 6 months and follow-up MRI and MRA at 6 months showed stable occlusion of VA with resolution of aneurysm. The 27 small aneurysms with narrow neck were treated with straight coiling of aneurysm with preservation of parent VA. These cases were not given antiplatelets or anticoagulation for reasons given above. For the two wide neck aneurysms and the two large aneurysms, which were treated early in the series, were managed with staged partial coiling followed by delayed stent-assisted coiling with Neuroform (Stryker Neurovascular, Fremont, California, USA) and Enterprise stents (Cordis Neurovascular, Miami, Florida, USA). For these four cases aspirin and clopidogrel were given for 5 days prior to stent placement and heparin was administered during the procedure. Subsequently the cases were maintained on aspirin and clopidogrel. At 6 months follow up all cases presenting with good WFNS grade achieved good outcome of mRS 0 to 2. Among the five cases who presented with WFNS grade four and five, two (40%) achieved good outcome. There was one death (3%) and two poor outcome (6%). Follow-up angiography at 6 months in all the cases who survived showed stable occlusion of aneurysms with no recurrence.

Treatment complications directly attributable to endovascular intervention include two symptomatic cerebellar infarcts (3%), one each in coiling of aneurysm and VA coil occlusion for dissecting aneurysm. There was no hemorrhagic complication. 12 cases (20%) required ventriculoperitoneal shunt insertion. One case who was on double antiplatelet therapy for flow diversion for dissecting aneurysm developed asymptomatic subcortical hemorrhage post-ventriculoperitoneal shunt insertion.

At 6 months follow up 50 cases (83%) achieved good outcome with mRS one to two. There were eight cases with poor outcome (13%) and two deaths (3%). The two deaths both presented with WFNS grade 5.

4. Discussion

Current endovascular treatment options for saccular VA aneurysms include direct coiling of aneurysm (with or without adjunct techniques such as balloon remodeling or neck bridging), intrasaccular devices, stent assisted coiling or flow diverter with or without coiling [3] [4]. Sometimes when there is anticipated need for CSF diversion procedure or surgical decompression, staged partial coiling followed by flow diverter or stent insertion and additional coiling (usual-

ly two to three weeks after hemorrhage) when the patient is able to tolerate double antiplatelets is done to minimize the risk of postoperative hemorrhagic complications. For giant aneurysms involving the non-dominant or co-dominant VA, coil occlusion without antiplatelets or heparin may be the simplest and safest solution because of the potential need for decompression due to the mass effect or the need for ventriculoperitoneal shunt [5].

For VA dissecting aneurysms the current endovascular options include deconstructive or reconstructive procedures. The risk of rebleeding for ruptured VA dissecting aneurysm is very high [6] [7]. Therefore, early intervention is paramount. Endovascular deconstructive techniques include proximal occlusion or endovascular trapping with balloons or coils. Coils are easier to control and will not deflate like balloons. Some reports incorporated balloon occlusion test prior to balloon or coil occlusion. In any case, detachable balloons are not available in many parts of the world [3] including the author's practice. Reconstructive techniques include flow diversion or stent placement with or without additional coiling. However, stent or flow diverter placement requires dual antiplatelet administration [3]. This could increase the risk of bleeding when surgical decompression or CSF diversion procedures are required [7] [8]. To date, the technique of choice for intervention of ruptured VA dissecting aneurysm remains controversial although in the current flow diverter era reconstructive techniques to keep the VA patent are gaining popularity. Unfortunately, early fatal rebleeding has been reported with these stent or flow diverter assisted endovascular reconstructive procedures [9]. Endovascular parent artery occlusion also has been reported to have a higher immediate postoperative occlusion rate, compared to stent assisted or flow diverter assisted techniques [10]. Therefore, when the anatomy is favorable (namely co-dominant or dominant contralateral vertebral artery and no involvement of PICA in the aneurysmal segment), endovascular parent artery coil occlusion has been the author's preferred option.

The outcome for this series is comparable to published literature. In this series, all ruptured saccular aneurysm cases with good WFNS grade at presentation had good outcome. Among the five cases who presented with WFNS grade four and five, two (40%) achieved good outcome. There was one death (3%) and two poor outcome (6%). All the cases who survived had angiographic stability at 6 months. For ruptured VA saccular aneurysm, Mericle *et al.* reported that of the patients who presented with a favorable clinical grade 87% had good outcomes at follow-up. Of the patients who presented with a poor clinical grade, 50% had good outcomes at follow-up. Angiographic occlusion was achieved in 97% of cases [4].

For VA dissecting aneurysms the outcome for this series (74% good outcome) is also comparable to published literature for parent artery occlusion, which was done in the majority of cases [10]-[15], where good outcomes were reported between 59% and 100% of cases. Our study, similar to Raper *et al.* [15] and Peluso *et al.* [14], showed no recurrence at follow-up, demonstrating durable effect of the simple treatment strategy.

It is worth noting that there were two cerebellar infarcts (3%) directly attributable to endovascular intervention in this series. It is tempting to consider using antiplatelet agent or anticoagulation in this setting to reduce thromboembolic complication. However, it is important to take note that the use of these agents may increase the risk of bleeding should the patient require surgical intervention, as had happened in one case in this series post ventriculoperitoneal shunt, albeit asymptomatic.

5. Conclusion

Good outcome can be achieved with endovascular treatment for ruptured VA aneurysms, even in some patients with poor WFNS grade at presentation. Parent artery occlusion is a safe, effective and durable treatment for ruptured VA dissecting aneurysms when the anatomy is favorable.

Conflicts of Interest

There is no conflict of interest to declare.

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Clinical Practice Guideline for the Management of Overweight and Obesity in Adults in Saudi Arabia

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Abstract

Obesity and overweight are prevalent in Saudi Arabia (24.95% & 31.80%). Also, childhood obesity in the country is a challenge, with 6% - 10% of preschool and school-age children. The burden of being overweight and obese is disastrous. Therefore, the Saudi Diabetes Scientific Society constituted a team to develop a guideline. The team reviewed the local Clinical Practice Guidelines for the Prevention and Management of Obesity in Saudi Arabia; and conducted a rigorous review of relevant evidence-based scientific literature. After a thorough assessment, a consensus was reached to use the Australian guideline as the main guideline to be adapted and localized to be suitable for the Saudi people. To avoid duplication of efforts, the team adopted the grading of evidence used by the Australian guideline. The updated version was

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presented in a workshop, and the recommendation of the participants was included. The final draft was distributed for review, and comments were included. This document presents the result of such an effort as a local guideline.

Keywords

Obesity, Overweight, Disease Burden, Management, Guideline, Saudi Arabia

1. Introduction

By 2030, one billion people will be obese worldwide, including one in five women and one in seven males, according to the World Obesity Atlas 2022. The prevalence of obesity worldwide has roughly tripled since 1975, according to the World Health Organization (WHO) fact sheets. Most people on the planet reside in regions where being overweight or obese kills more people than being underweight. In 2016, there were 41 million under five years old children who were overweight or obese. Also, there were approximately 340 million overweight or obese children and teenagers between the ages of 5 and 19. However, obesity is a disease that may be prevented [1] [2].

The prevalence of obesity in Saudi Arabia (KSA) was demonstrated in a recent systematic review and meta-analysis (2020), which investigated obesity and overweight among adults in Middle East Countries from 2000 to 2020. The prevalence of obesity in KSA was estimated to be 24.95% (95% CI: 21.02% - 29.61%), and for overweight, it was 31.80% (29.56% - 34.21%). According to the data from the World Atlas, KSA is the world's 14th most obese country, with an overall obesity rate of 35.4% [3] [4] [5]. These rates are less than what was forecasted by ***Al-Quwaidhi et al.*** to be 41% & 78% in men and women, respectively, by 2022 [6]. A serious challenge affecting the country is the rise in childhood obesity which is affecting approximately 6% - 10% of preschool and school-age children [7].

Obesity is considered an inheritance of societal modernization with faulty dietary habits, unhealthy food, less physical activity, and increased stress. These deviations are extreme in the last four decades because the daily per capita consumption was increased by 143.3% [5] [8]. Also, the escalation in the prevalence of obesity is directly contributed by environmental and behavioral factors, rather than biological factors. It is also influenced by ethnic diversity. Due to high-fat diets and more sedentary lives, people in metropolitan regions have higher obesity rates than those in rural areas [5].

Saudi Arabia has a serious obesity problem. An increase in obesity and overweight, which are key risk factors for various other diseases like hypertension, diabetes, obstructive sleep apnea, hyperlipidemia, and osteoarthritis, is indicated by previous studies on the prevalence of obesity in the KSA [8] [9] [10] [11].

Increased BMI is a significant risk factor for non-communicable diseases such as osteoarthritis, diabetes, cardiovascular disease, and several malignancies. Additionally, there is a link between childhood obesity and a higher risk of adult obesity, early mortality, and disability. Additionally, breathing issues, a higher incidence of fractures, hypertension, early indicators of cardiovascular disease, insulin resistance, and psychological consequences are all experienced by obese children [1].

The cost of being overweight and obese in KSA was calculated from a social perspective in the study by Malkin *et al.* (2022). Six major non-communicable illnesses' costs associated with being overweight or obese were assessed. The direct costs of overweight and obesity for these disorders are estimated to be $3.8 billion, or 4.3 percent of KSA's overall healthcare expenditures in 2019. In 2019, it was predicted that overweight and obesity-related absenteeism and presenteeism would cost $15.5 billion, or 0.9 percent of Gross domestic product (GDP). The results show that excess weight and obesity represent a considerable economic burden in KSA, even when the study is restricted to six disorders and a subset of all indirect expenses [12].

2. Guideline Development Process

Scope and objective: This guideline handles the following areas: Increase the awareness of society with the magnitude of the problem and its hazard; prevention using screening of high-risk individuals; management of lifestyle changes, drugs, and surgical interventions. The guideline aims to provide recommendations for the prevention and management of overweight/obesity based on current evidence for best practices that are suitable for our society, culture, and healthcare system. Clinical question to be answered is presented in **Table 1**.

Development process: The Saudi Diabetes Scientific Society constituted a team to develop the guideline. They reviewed the local Clinical Practice Guidelines for the Prevention and Management of Obesity in Saudi Arabia; and also conducted a rigorous review of relevant evidence-based scientific literature. After a thorough assessment, a consensus was reached to use the Australian guideline as the main guideline to be adapted and localized to be suitable for the Saudi people (**Table 2**). To avoid duplication of efforts, the team adopted the grading of evidence used by the Australian guideline used in this document. The updated version was presented in a workshop, and the recommendations of the participants were included. The final draft was distributed for review, and comments were included [14].

Update of the guidelines: Updating the guideline will be considered every three years.

3. Assessment for Overweight or Obesity

Key messages

- Assessing adults for overweight or obesity enables the identification of people who may benefit from weight management and/or intervention advice.

Table 1. Clinical question to be answered: Following PIPOH tool was used before adaptation [13].

The **P**opulation concerned and disease condition:	The **I**nterventions of interest:
The target population includes all adult people from different gender and age groups.	– Screening the population for overweight and obesity. – Assessment of overweight and obesity. – Psychological, dietary and physical exercise interventions. – Different management options for people with overweight or obesity: pharmaceutical and surgical.
The **P**rofessionals to whom the guideline will be targeted:	The expected **O**utcome including patients, public and system outcome:
This guideline is intended for the use of healthcare experts at all levels, including physicians, nurses, dietitians, psychologists, and physiotherapists.	To reduce the prevalence of overweight and obesity and their co-morbidities. To reduce the expenditure of the health system. To decrease the variations in clinical practice.
The **H**ealth care setting and context in which the guidelines are to be implemented:	
Primary healthcare units and hospitals.	

Table 2. Evidence matrix [14].

Evidence matrix	Excellent [A]	Good [B]	Satisfactory [C]	Poor [D]
Evidence base	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias.	One- or two-level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias.	One- or two-level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias.	Level IV studies, or level I to III studies/SRs with a high risk of bias.
Consistency	All studies consistent.	Most studies consistent and inconsistency may be explained.	Some inconsistency reflecting genuine uncertainty around clinical question.	Evidence is inconsistent.
Clinical impact	Very large	Substantial	Moderate	Slight or restricted

Continued

Generalizability	Population/s studied in body of evidence are the same as the target population for the guideline.	Population/s studied in the body of evidence are similar to the target population for the guideline.	Population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population.	Population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalize to target population.
Applicability	Directly applicable to Saudi healthcare context	Applicable to Saudi healthcare context with few caveats	Probably applicable to Saudi healthcare context with some caveats	Not applicable to Saudi healthcare context

BMI = body mass index; kg/m^2 = kilograms per square meter.

- Routine BMI and waist circumference assessment is used to identify overweight and obesity.
- Assessing for the risk or presence of comorbidities that may be influenced by being overweight and obese allows for overall risk to be estimated and for conditions to be managed together.
- Asking about other contributors to weight gain (certain medications, quitting smoking) and weight history (including previous weight loss attempts) should also be part of the assessment of people who are overweight or obese.
- Discussing a person's readiness for behavioral change involves talking about the person's interest and confidence in making changes, as well as the benefits and difficulties of weight management.

The main objective of the assessment is to identify those with overweight and obesity among people.

1) Should we start by all individuals? Not everyone is willing to have their weight or obesity evaluated. There are numerous social or personal elements that have an impact on how people see weight evaluation. Any effective approach to a specific health issue must include awareness as a major element. Increasing awareness through various media platforms is a wise move [14].

2) Should we discuss hazards due to overweight or obesity? A very crucial point about obesity is its psychological and social impact on life. Overweight or obese people often have a history of dealing with frustrating problems and may have experienced social discrimination. Discussing the entire spectrum of hazards due to obesity, from physical to psychological and social health, is tremendously important because this will increase awareness of the problem and motivate people to seek medical help. Having a conversation about weight evaluation

with those who are at ease doing so utilizing effective communication techniques to build rapport with them and set the right tone. Do not pass judgment and acknowledge the impact of social context on health behaviors. Do not use words that are stigmatizing or discriminating. Describe how weight evaluation is a common practice. Inform them that measuring their height, waist, and weight is part of the process of determining their weight. Explain how BMI is calculated using a person's weight and height. Let them know that BMI and waist size are used to determine their risk of developing diabetes and heart disease. Obtain the subject's permission before taking a weight or height reading. Anytime you need to improve your communication, enlist the aid of other experts (such as interpreters or multicultural health workers). The World Health Organization and international obesity guidelines recommend BMI as the primary indicator [15] [16] [17] [18] [19]. The BMI cutoffs are the same for men and women. At the individual and population level, it is generally accepted practice to measure weight, height, and calculate BMI. The BMI calculator is one of the health tools that the Saudi Ministry of Health has issued [20].

***Recommendation* 1:** *Use BMI to classify overweight or obesity in adults. B Weight and height measurement*

***To measure the weight*:** Use a regularly calibrated scale on a hard, level surface. Ask the person to remove shoes and heavy outer garments (coat, jacket). Ask the person to stand centered on the scale with weight evenly on both feet. Record the weight. If the person weighs more than the scale can measure, note this and the upper limit of the scale.

***To measure the height*:** Use a height rule taped vertically to a hard, flat wall, with the base at floor level. Ask the person to remove their shoes, heavy outer garments, and hair ornaments. Ask the person to stand with his or her back to the height rule. The back of the head, back, buttocks, calves, and heels should be touching the wall and the person's feet together. Ask the person to look straight ahead. Press hair flat and record height. If the person is taller than the measure, the measurer should use a platform to avoid parallax error [21].

Calculating the BMI: BMI is calculated by dividing weight (kg) by the square of height (m^2).

Classifying the BMI: According to the WHO classifications, an adult's BMI can be categorized as being underweight, of normal weight, overweight or obese (3 subclasses) as shown in **Figure 1** [19].

Interpreting the BMI: When BMI exceeds 30 kg/m^2, increased mortality and a greater incidence of disease linked to increased fat mass are most pronounced at the community level. When determining healthy weight in specific populations where there is variability in muscle and fat mass, the BMI may occasionally be less accurate. We should consider the following factors: Individuals with the same BMI may have different ratios of body fat to lean mass. *Athletes* (high muscle mass) may have a lower proportion of body fat, so a higher BMI threshold can be considered. *Women* have more body fat than men at the same BMIs. *Elderly* people will have more body fat than younger ones at the same

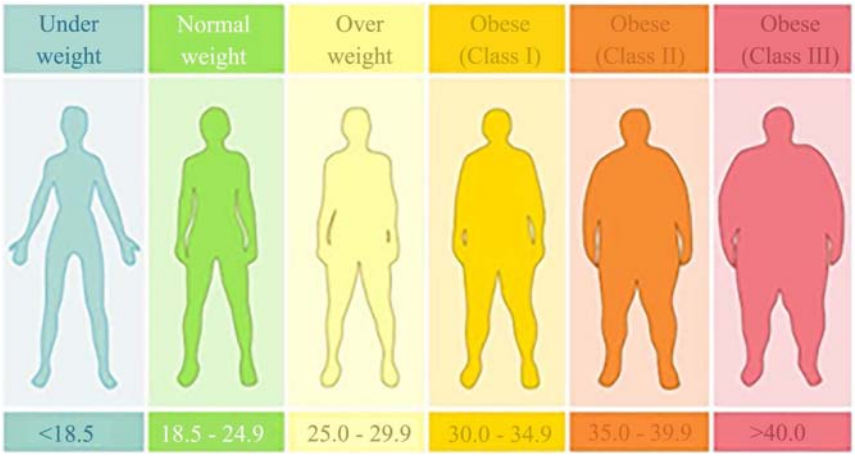

Figure 1. Obesity classes.

BMI. *South Asian*, *Chinese*, *and Japanese population groups* may have more body fat at lower weights and be at greater risk of ill-health than people from other population groups, so consider a lower BMI threshold (e.g., >23 kg/m^2). *Central* (*or abdominal*) *fat distribution* increases health risks. Also, central deposition of fat and decreased muscle mass with age may lead to no overall change in weight or BMI but an increase in health risk [17] [22]-[27].

Waist circumference: It is a reliable indicator of visceral fat and a decent sign of total body fat. It is a more accurate predictor of cardiovascular risk, type 2 diabetes (in women but not in men), and metabolic syndrome when compared to BMI. According to current standards, measuring waist circumference is advised as part of the evaluation for absolute cardiovascular and type 2 diabetes risk in order to enhance the prognosis of some chronic conditions [28]-[37].

***Recommendation* 2:** *Use waist circumference in addition to BMI to help adults better assess their risk of developing comorbidities associated with obesity. C*

How to measure an adult's waist circumference: Use a measuring tape that is checked monthly (replace if stretched). Request that they take off any heavy outerwear, take any belts off, and empty their pockets. As the person stands, ask them to evenly distribute their weight on both feet and to breathe properly while keeping their feet about 12 to 15 cm apart. Wrap the measuring tape horizontally at a level that is halfway between the lower rib edge and the iliac crest while maintaining a firm grip on it (approximately in line with the umbilicus). The finger should fit between the tape and the body if the tape is sufficiently loose. Keep track of the measurement made during an exhale.

Identifying risk level associated with waist circumference: In general, gender and ethnicity affect the cutoff point at which waist circumference indicates elevated or high disease risk:

Women's risk increases at 80 cm and reaches a peak at 88 cm, while men's risk increases at 94 cm and reaches a peak at 102 cm [38]. Thresholds of 90 cm for males and 80 cm for women are linked to a significantly higher risk of meta-

bolic problems in **South Asian, Chinese, and Japanese** individuals [33]. Waist circumference is not a reliable indicator of body fat in some circumstances (such as pregnancy or certain medical illnesses that cause abdominal distension).

Other factors in assessment of health risk in adults: It has been previously noted how genetic, familial, and life stage factors—which enhance the tendency to be overweight and obese—play a role. A person's weight history, readiness to adopt new health behaviors and comorbidities that may be influenced by overweight and obesity are additional factors that are relevant to the assessment of health risk. Other factors also include dietary intake and physical activity, as well as factors that may influence these behaviors.

Current health behaviors: It might be difficult to evaluate how healthy behaviors affect weight. It is important to consider how an individual's ability to follow health advice is influenced by their eating and physical activity patterns (such as being physically active but binge eating frequently), **Table 3**.

Risk or presence of physical comorbidities: Cardiovascular illnesses and their related risk factors (elevated blood pressure and lipids), type 2 diabetes, and various malignancies provide the biggest health hazards for people who are overweight or obese. The requirement for weight management is greater when comorbidities are present. Obesity is linked to a higher cardiovascular death rate. In addition to making a person's chronic conditions, such as type 2 diabetes and arthritis, more difficult to manage, being overweight can also speed up the progression of existing conditions [39] [40] [41].

Assess cardiovascular risk and diabetes: In adults aged 35 years and over, assess for cardiovascular risk. In aged 35 and over, Screen for undiagnosed diabetes. Screen for undiagnosed diabetes in individuals at high risk [42]: People with impaired glucose tolerance or impaired fasting glucose. People aged 35 years and over with BMI $\geq$ 30 kg/m^2 or hypertension. Adults with clinical cardiovascular disease (myocardial infarction, angina, stroke, or peripheral vascular disease). Women with polycystic ovary syndrome who are obese. People on antipsychotic medications.

Assessment should also include other physical comorbidities associated with excess weight, including: 1) Symptoms of sleep apnea (snoring, frequent waking, daytime hypersomnolence), 2) Signs of arthritis, especially in the hip and knee joints, 3) Symptoms of gastroesophageal reflux disease (GERD), 4) Assessment of right-heart function for evidence of pulmonary hypertension or right-heart failure, and 5) Polycystic ovary syndrome.

Mental health comorbidities like depressive disorders and eating disorders are associated with being overweight and obese. If these disorders are suspected, referral to a psychologist for mental health assessment is advisable. **1) Depressive disorders:** symptoms of depression include: a) depressed mood most of the day, b) loss of interest or pleasure in usual activities, c) weight loss or gain (when unintended), d) insomnia or hypersomnia, e) slowed or agitated movements, f) fatigue or loss of energy, g) feelings of worthlessness or guilt, h) diminished ability to concentrate or indecisiveness, and i) recurrent thoughts of death, suicidal

Table 3. Inquiries to make when evaluating health-related behaviors.

Dietary behavior	
1) Does the person consume healthy foods (as per Saudi Dietary Guidelines)? 2) Does the person consume high-energy foods or soft drinks? 3) What are the person's eating patterns (regular meals, snacking, restriction, binge eating)? 4) What is the person's attitude to dietary behavior?	
Physical activity	
1) What is the person's level of: a) Sedentary activity? b) Incidental activity? c) Moderate-intensity activity (frequency, duration)? d) Vigorous activity (frequency, duration)? 2) What is the person's attitude towards physical activity?	
Social influences on health behaviors	
Cultural background	Are attitudes to health behaviors influenced by cultural values?
Access to healthy foods	Are healthy foods locally available and affordable? Does the person have the means to store foods appropriately?
Education	Does the person understand healthy behaviors (e.g. high-energy versus low-energy foods, recommended levels of activity)?
Opportunities for physical activity	Does the person have time and support (e.g. child care)? Does the local environment support physical activity (e.g. walking tracks)?
Psychosocial support	Are the person's family and/or friends supportive of healthy behaviors?
Physical and developmental factors	
Comorbidities	Is the person on medications associated with weight gain?
Fitness	Is fitness level sufficient for moderate-intensity activity?
Mobility	Is mobility impaired (e.g. due to age, obesity or comorbidities)?
Physical disability	Is activity impeded by disability?
Intellectual disability	Is lifestyle change impeded by disability?
Psychological factors	
Life stressors	Has the person experienced life stressors (e.g. abuse, trauma, grief)?
Mood disorders	Is the person experiencing symptoms of depression?
Disordered eating	Is the person experiencing or at risk of an eating disorder?
Serious mental illness	Is the person on medications associated with weight gain?
Lifestyle	Does the person wish to change other behaviors (e.g. smoking)?

thoughts [43]. **2) Eating disorders:** the following questions may assist in assessing if an adult has or is at high risk of an eating disorder: a) do you think you have an eating disorder? And b) do you worry about your shape and weight? Screen for eating disorders by the SCOFF questionnaire (**Table 4**) [44] [45].

Factors that may contribute to weight gain

Medications: Some medications may cause considerable amounts of weight gain in relatively short amounts of time (**Table 5**). Conversely, some medications that have been associated with weight gain—combined contraceptives and hormone replacement therapy—appear not to result in weight gain. When medications associated with weight gain are required to treat comorbidities, specific advice, and support for weight loss should be provided. Substitution with an alternative medication or a change in dosage can be considered [46] [47] [48].

Quitting smoking: People who quit smoking for at least one-year experience greater weight gain and increased waist circumference than those who continue to smoke. The amount of weight gain after smoking cessation may differ by age, social status, and certain behaviors. A Cochrane review of interventions to prevent weight gain after smoking cessation found that individualized interventions, very low-energy diets, and cognitive behavioral therapy may reduce weight gain associated with smoking cessation without affecting quit rates. Additionally, exercise interventions may be effective in the longer term (12 months). General advice to avoid weight gain has not been found to be effective and may reduce quit rates. The health benefits of smoking cessation are broad and are likely to outweigh the risks of weight gain [17] [38] [49] [50] [51].

Table 4. The SCOFF questions.

1) Do you make yourself **S**ick because you feel uncomfortably full?
2) Do you worry you have lost **C**ontrol over how much you eat?
3) Have you recently lost more than **O**ne stone (6 kg) in a 3-month period?
4) Do you believe yourself to be **F**at when others say you are too thin?
5) Would you say that **F**ood dominates your life?
*One point for every "yes"; a score of ≥2 indicates a likely case of anorexia nervosa or bulimia. A further two questions have been shown to indicate a high sensitivity and specificity for bulimia nervosa. These questions indicate a need for further questioning and discussion.
1) Are you satisfied with your eating patterns?
2) Do you ever eat in secret?

Table 5. Medications associated with weight gain at 12 weeks from commencement [46].

Atypical antipsychotics: (clozapine, olanzapine)—Lithium	Tricyclic antidepressants (amitriptyline)
Beta-adrenergic blockers, particularly propranolol	Pizotifen
Sodium valproate	Anabolic steroids
Sulphonylureas: (chlorpropamide, glibenclamide, glimepiride and glipizide)	Insulin Thiazolidinediones (pioglitazone)

Weight history: Advice on weight management will differ depending on the number of previous weight loss attempts and the degree of overweight or obesity. Weight history, including previous weight loss attempts, should be part of the assessment of people who are overweight or obese. Discuss the following relevant areas to assess weight history: 1) Age of onset of overweight or obesity? 2) Family history of obesity? 3) Any history of eating disorders, symptoms of eating disorders (e.g., binge eating), or unhealthy weight loss methods (e.g., misuse of laxatives, self-induced vomiting)? 4) Weight stability, and for how long has the person been at this present weight? 5) What have been the maximum and minimum weights? 6) What attempts at weight loss have been made in the past? Have any worked? 7) If not, why does the person think they were unsuccessful? 8) If so, what attempts were made to maintain the new lower weight? Did this work, and for how long? 9) What is the person's understanding of the reasons or triggers for weight gain/regain? 10) Has weight loss medication been tried? 11) Has the person had weight loss surgery? 12) Has the person seen other professionals or organizations for weight loss?

Weight cycling: The weight history may indicate previous weight cycling—that is, repeated intentional loss and subsequent regain of weight (usually around 4.5 kg). There is debate about whether weight cycling promotes obesity and/or increases cardiovascular risk. Concerns about the possible harms of weight cycling do not outweigh the benefits of losing weight. A focus on sustainable (rather than restrictive) changes in dietary behavior may support motivation and reduce the likelihood of continuing weight cycling and other potential health effects (e.g., eating disorders) [52] [53].

Readiness to change: Consider the person's willingness to undertake the behavioral change because it is required for effective weight management. Algorithms that attempt to stage readiness to change may be more effective if tied explicitly to the specific behaviors (**Table 6**). Rather than simply asking whether the person is ready to change health behaviors, it may be helpful to begin by assessing his or her interest and confidence in change [54] [55] [56]. This can be followed by a discussion of the benefits and difficulties of making lifestyle changes and whether the person is interested in looking at ways to improve health. Some sample questions that can be used to assist people in identifying their readiness to change are:

***Recommendation* 3:** *For adults who are overweight or obese, discuss readiness to change lifestyle behaviors. D*

Readiness to change lifestyle behaviors may be identified during routine consultation—however, it is unclear whether available tools for assessing readiness to change are helpful in predicting change or weight loss. While health professionals make judgments based on an individual's answers to a series of questions, there may be time and cost implications from longer consultations. Active management of an individual who may not be ready to engage may also have cost and resource implications. While referral and follow-up appointments to discuss weight management options have cost implications for individuals, a

Table 6. Discussing readiness to change [57].

Intention to change	How important do you think it is for you to make changes at the moment?
Skills and self-confidence	How confident are you that you can change your eating patterns and increase your physical activity to improve health?
Obstacles to change	Are there any stressful events in your life now that might get in the way?
Positive feelings about change	Do you feel you can succeed in changing health behaviors, and how much do you believe it is worth the effort?
Self-image and group norms	Can you picture yourself changing health behaviors? How do you think your friends and family will react to your efforts?
Encouragement and support	Are there people who can support you to change health behaviors? Do you think they will help you in your efforts?

referral could be made directly to practice nurses or other providers if there are no additional perceived comorbidities. Techniques for motivational interviewing and discussing readiness to change could also be an identified training need for healthcare professionals.

4. Counselling for People with Overweight or Obesity

Key messages

- Even small amounts of weight loss bring health benefits, including lowered cardiovascular risk, prevention, delayed progression or improved control of type 2 diabetes, and improvements in other health conditions.
- Lifestyle change that includes reduced energy intake and increased physical activity has health benefits independent of weight loss.
- Overweight and obesity are associated with a wide range of other conditions, particularly cardiovascular disease, type 2 diabetes, and some cancers. The risk of comorbidity appears to rise with increasing BMI.

Explaining the benefits of lifestyle change and weight loss, even if modest, increases awareness and drive motivation in overweight and obese people. **These health benefits are:**

1) ***Reduction of cardiovascular risk by***: Systolic blood pressure reduction with weight loss of at least 2 kg [A], small improvements in lipid profiles with sustained weight loss [A], and reduction of cardiovascular and all-cause mortality [C] [58]-[68].

2) ***Prevention and improved control of type 2 diabetes*** **[*A*]** [60] [64] [68]-[85]

3) ***Improvements in other conditions***: Improvements in markers of chronic kidney disease [B] and reduction in obstructive sleep apnea [B] [86] [87] [88]

[89] [90].

4) ***Improves symptoms of some conditions*****:** Improvements in symptoms of gastro-esophageal reflux disorder [C]. Reduced stress incontinence in women [C]. Reduced knee pain with moderate weight loss (6 kg) in adults with osteoarthritis [C]. Improved functional mobility and physical performance in older people [B] [91]-[98].

5) ***Improvements in quality of life, self-esteem and depression,*** even if weight loss is not substantial. C [63] [97] [98] [99] [100] [101].

Not everyone is willing to have their weight or obesity evaluated. There are numerous social or personal elements that have an impact on how people see weight evaluation. As part of routine care, individuals who are overweight or obese should be told about the advantages of losing weight. For the patient and the healthcare professional, referral, the creation of treatment plans, and ongoing monitoring are likely to have cost and time implications.

***Recommendation* 4:** *Adults who are overweight or obese can be strongly advised that modest weight loss reduces cardiovascular risk factors. A*

***Recommendation* 5:** *Adults with prediabetes or diabetes can be strongly advised that the health benefits of modest weight loss include prevention, delayed progression, or improved control of type* 2 *diabetes. A*

***Recommendation* 6:** *Adults with kidney disease or sleep apnea can be advised that improvements in these conditions are associated with a* 5% *weight loss. B*

***Recommendation* 7:** *Adults with musculoskeletal problems, gastro-esophageal reflux, or urinary incontinence can be advised that weight loss of* 5% *or more may improve symptoms. C*

***Recommendation* 8:** *Adults who are overweight or obese can be advised that quality of life, self-esteem, and depression may improve, even with small amounts of weight loss. C*

Explaining the health risks associated with overweight and obesity: Type 2 diabetes, cardiovascular disease, and various malignancies are the main illnesses for which obesity predicts greater mortality and/or morbidity. Additionally, musculoskeletal, reproductive, and mental health issues are all highly correlated with obesity (**Table 7**).

Life expectancy: Numerous studies suggest a connection between obesity and being overweight and a shorter life expectancy. People who were obese (BMI 30 - 35 kg/m^2) died 2 - 4 years earlier than those who were at an optimal weight, according to a big study (n = 900,000). In comparison to the effects of lifelong smoking, a BMI of 40 - 45 kg/m^2 resulted in a loss of 8 - 10 years of life expectancy. Another study that estimated the impact of obesity on life expectancy (starting at age 40) discovered a mean loss of 7 years, which is comparable to the loss of life expectancy from smoking [102] [103] [104] [105] [106].

Comorbidities: There is mounting proof that being overweight or obese increases the risk of developing a number of comorbidities. Starting at BMIs of approximately 20 - 21 kg/m^2, the relationship between BMI and many of these

Table 7. Health risks associated with overweight and obesity in adults [39] [87] [107]-[132].

Cardiovascular	Gastrointestinal
1) Stroke 2) Coronary heart disease 3) Hypertension	1) Gallbladder disease 2) Gastro-esophageal reflux disease 3) Hepatic, biliary and pancreatic disease 4) Cancers of the bowel, esophagus (adenocarcinoma), gall bladder and pancreas.
Endocrine	
Type 2 diabetes	
Genitourinary	**Reproductive health**
1) Chronic kidney disease 2) End-stage renal disease 3) Kidney cancer 4) Glomerulopathy 5) Kidney stones 6) Stress urinary incontinence (women)	1) Menstrual disorders 2) Miscarriage and poor pregnancy outcome 3) Infertility/subfertility 4) Breast cancer (postmenopausal women) 5) Endometrial cancer 6) Ovarian cancer
Pulmonary	**Musculoskeletal**
1) Obstructive sleep apnoea 2) Asthma	1) Osteoarthritis 2) Spinal disc disorders Lower back pain Disorders of soft-tissue structures such as tendons, fascia and cartilage 3) Mobility disability (particularly in older adults) 4) Impaired immune function
Mental health	
1) Depression 2) Anxiety disorder 3) Reduced health-related quality of life 4) Disordered eating	

disorders appears to be constant. The increased risk of cardiovascular illness experienced by those who are overweight or obese is a result of the relationship between BMI and cardiovascular risk factors (blood pressure, lipids, type 2 diabetes) [18] [39].

5. Applying a Multi-Component Multi-Disciplinary Therapeutic Approach

Key messages

- Multicomponent interventions that address all three lifestyle areas related to overweight and obesity—nutrition, physical activity, and psychological approaches to behavioral change—are more effective than single-component interventions.
- Lifestyle approaches should focus on creating an energy deficit. This can be achieved through reducing energy intake, increasing energy expenditure, or both. Creating an energy deficit needs to be supported by measures to assist behavioral change.
- For many overweight and most obese adults, achieving a "healthy" weight is an unrealistic expectation—a weight loss of 5% is achievable and will result in health benefits. Treatment goals should focus on behavioral change and improved health.

- More intensive weight management interventions—such as very low-energy diets, weight loss medication, and bariatric surgery may need to be considered as adjuncts to lifestyle approaches, especially when a person is obese and/or has risk factors or comorbidities or has been unsuccessful reducing weight using lifestyle approaches. The decision to use intensive weight loss interventions is made based on the individual situation.
- Individuals should be well informed and supported in changing health behaviors and be assisted in managing overweight and obesity in partnership with one or more healthcare professionals. Interventions need to be individualized and supported by self-management principles and regular review by a healthcare professional.
- Influences on health behaviors (e.g., social, physical and psychological factors) should be considered when planning interventions with individuals.

Lifestyle interventions: Nutrition, physical activity, and behavioral change are the three main lifestyle factors associated with being overweight and obese. Interventions with several components—those that deal with all three areas—are more effective than those that merely deal with one or two of them. However, it is challenging to produce evidence to determine what sort and how many interventions should be included in a multi-component intervention for weight loss. Depending on the context, the person, and the implementation resources available, each component may have proof of its efficacy and be suitable for inclusion into a multi-component intervention. A lifestyle intervention may involve testing out several combinations of strategies to find the one that works best and is most sustainable for each person. The delivery of lifestyle-based interventions in primary healthcare is well-suited. In some circumstances, a referral to other services (such as a dietician, psychologist, or exercise physiologist) may be necessary. A change in lifestyle that includes less energy intake and more exercise has a number of advantages independent of weight loss. For instance, lifestyle adjustments may enhance the quality of life even if weight loss is not achieved. Also, increased physical activity without weight loss can reduce cardiovascular risk factors, improve functional mobility in older people and reduce glycated hemoglobin (HbA1c) by approximately 0.6% in adults with type 2 diabetes [62] [63] [82] [96] [97] [98] [133].

Recommendation 9: *For adults who are overweight or obese, strongly recommend lifestyle change—including reduced energy intake, increased physical activity, and measures to support behavioral change. A*

Healthy lifestyle options should be discussed routinely with individuals who are overweight or obese. Referral and continued monitoring are likely to have cost and time implications for the individual and healthcare professional. Specific lifestyle changes and plans can be discussed and developed with GPs, practice nurses, and other healthcare professionals. There may be cost implications, availability, and access issues associated with each. Monitoring of any comorbidities should continue to be done by the GP or a relevant member of a multidis-

ciplinary approach. Healthy life style is encouraged and demonstrated in details by the Saudi Ministry of Health (MOH). [134]

Reducing energy intake: Several dietary interventions can produce weight loss, including low-carbohydrate diets and low-fat diets. These Guidelines do not discuss specific dietary interventions, as the evidence of their effectiveness was not considered in the systematic literature review [3]. Healthy eating habits and Saudi healthy food proportions are demonstrated by the Saudi MOH [135].

Healthy dietary patterns: The Saudi Dietary Guidelines summarize the evidence underlying food, diet, and health relationships that improve public health outcomes and highlight dietary patterns that promote health and well-being as well as reduce the risk of chronic disease. Current Saudi Dietary Guidelines should be used as the basis of advice on nutrition for adults [136].

Dietary approaches to weight loss: Dietary interventions should be designed to create an energy deficit, suit the needs and preferences of individuals, and include a wide variety of nutritious foods as recommended in the current Saudi Dietary Guidelines. In some situations (e.g., when comorbidities are present), referral to a dietitian may be needed for guidance on developing an eating plan that is suitable to the individual's needs [136].

***Recommendation* 10:** *Design dietary interventions for weight loss in individuals who are overweight or obese to result in a* 2500 *kilojoule energy deficit per day, and customize programs to the individual's dietary preferences. A*

While general practitioners (GPs) can suggest broad dietary adjustments, the creation of a customized program to induce an energy deficit may be more economically advantageous if provided by an accredited practicing dietitian. It is recognized that some places may have restricted access to certified dietitians. Greater access to dietician services might be made possible by methods like teleconferencing or videoconferencing. Specific tools, such as Life scripts, can help with management and referral. The cost of referral alternatives and the availability of particular service providers may have an impact on the individual. Additionally, finding the right foods for the person and family may provide problems with cost, equity, and access [137].

Discussing dietary approaches to weight loss: When discussing and recommending a particular approach, consider the individual context, including: 1) A degree of overweight or obesity (e.g., if there is a need for rapid weight loss, a very low-energy diet may be appropriate), 2) Dietary preferences of the individual and their family, 3) Their food supply (taking into account availability, affordability and capacity for appropriate storage of healthy foods), 4) Benefits of finding an eating plan that can be sustained (e.g., gradually changing eating habits), and 5) History of or current eating disorder.

People who are making changes to dietary behaviors as part of a weight management program may benefit from advice on healthy foods and eating patterns. Areas for discussion: **Practical information to support healthy eating include:** 1) General advice on healthy eating as outlined in the Saudi Dietary Guidelines, 2) The energy content of commonly eaten foods and drinks (e.g., books or web-

sites that list kilojoule content), 3) Recommended portion sizes, and strategies for controlling or reducing them (e.g., use smaller plates), 4) The need to reduce (rather than restrict) intake of foods that are high in energy (e.g., fats, sugar) and increase intake of foods that are low in energy but rich in other nutrients (e.g., vegetables, fruit), 5) Benefits of starting with small changes and avoiding situations that encourage unhealthy behaviors, 6) Examples of healthy foods that are affordable and familiar, or suitable alternatives, 7) Ways to identify and manage triggers for emotional eating, and 8) The importance of regular eating patterns and mindful eating [136].

Increasing physical activity: Physical activity is any bodily movement produced by skeletal muscles that expend energy. This includes activities that use one or more large muscle groups for movement in the following domains (**Table 8**): 1) Occupation, including paid and unpaid work, 2) Leisure, including organized activities such as sports, as well as exercise and recreational activities; and 3) Transport—for example walking, cycling or skating to get to or from places.

Different intensities of physical activity:

Physical activity recommendation of the Saudi MOH can be considered as a guidance for types of physical exercises that can be done [138]. Recommend moderate-intensity and vigorous activities that provide health benefits for adults aged 18 - 64 years. More recent evidence suggests that in most cases, the relationship between physical activity and health benefits is direct and curvilinear, with the greatest benefit seen in those who change from doing the least or no physical activity to doing more. The repeated physiological and metabolic adaptations, and energy expenditure associated with daily physical activity, make it likely that frequent activity is more beneficial than activity on only one or two days each week. Health benefits are achieved with around 150 - 300 minutes of moderate-intensity activity or 75 - 150 minutes of vigorous activity (or a combination of moderate-intensity and vigorous activity) each week [139]. Physical

Table 8. Levels of intensity of physical activity [18] [137].

Intensity	Description	Example
Sedentary	Activities that involve sitting or lying down, with little energy expenditure.	Occupational (e.g., sitting at work) Leisure (watching TV, reading, sewing, computer use for games, social networking) Transport (e.g., sitting in a car, train or bus).
Light	Activities that require standing up and moving around, in the home, workplace or community.	Housework (hanging out washing, ironing, dusting) Working at a standing workstation.
Moderate	Activities that requires some effort, but allow a conversation to be held.	Brisk walking, gentle swimming, social tennis.
Vigorous	Activities that lead to harder breathing, or puffing and panting (depending on fitness).	Aerobics, jogging and some competitive sports.

activity at the upper end of this range is required for the prevention of weight gain and to reduce the risk of breast and colon cancer. Muscle-strengthening activities are important for metabolic and musculoskeletal health (including maintaining bone density) and for maintaining functional status and the ability to conduct activities of daily living in older age, with significant benefits from muscle-strengthening activities twice weekly on nonconsecutive days. Prolonged sitting time is associated with an increased risk of premature death and a range of chronic health problems [140] [141] [142] [143] [144].

Physical activity: Although it is accepted that physical activity is integral to weight management, the evidence for a specified duration and intensity of exercise is unclear, given high individual variability in baseline levels of activity, eating patterns, medication use, and other lifestyle factors and comorbidities. Studies that focus on the association between physical activity and weight loss have found that increasing physical activity has a range of health benefits even if no weight is lost. Physical activity has little effect on weight unless it is combined with dietary changes. A dose-response exists between amounts of activity and weight loss. Maintaining high levels of physical activity (approximately 60 minutes per day) combined with other behavioral strategies may reduce weight regain. Gradually increasing activity levels are associated with fewer injuries in inactive adults [62] [63] [64] [65] [141]-[146]. The degree of overweight or obesity, fitness level, comorbidities and age are other considerations in prescribing physical activity. Accredited exercise physiologists can provide screening and stratify risks to ensure the safety and appropriateness of physical activity interventions.

***Recommendation* 11:** *For adults who are overweight or obese, prescribe approximately* 300 *minutes of moderate-intensity activity*, 150 *minutes of vigorous activity, or an equivalent combination of moderate-intensity and vigorous activities each week combined with reduced dietary intake. Consensus-based*

Brief advice on physical activity, delivered through primary health care in person, or by phone or mail, for sedentary people at risk of developing disease has a small beneficial effect and has been shown to be cost-effective. While tools such as **Life scripts** can help with physical activity assessment and prescription, exercise referral schemes may also provide a cost-effective option if no in-house program is available. Costs to the individual will vary depending on the selection of physical activity type that is appropriate, accessible, and likely to be sustainable. If functional mobility is an issue, referral to an exercise physiologist or physiotherapist may also incur costs to the individual and healthcare system. For adults who are overweight or obese, particularly those who are older than 40 years, there should be an individualized approach to increasing physical activity [147] [148].

Discussing physical activity: When discussing changes in physical activity, consider the following: 1) The health benefits of an active lifestyle, many of which are independent of weight loss, 2) The counterbalance of reducing sedentary activities (e.g. watching television, using computers), 3) tHe importance of avoiding prolonged periods of sitting (e.g. taking breaks from desk-based activi-

ties by standing or walking when on the telephone), 4) Appropriate forms of moderate-intensity activity for the person's current mobility (e.g. hydrotherapy may be more suitable for people experiencing weight-related joint pain), 5) Increasing incidental activity also contributes to health and weight management, 6) Clear and realistic goals, and relevant support mechanisms to increase the likelihood of activity being maintained on a long-term basis (e.g. regular interactions with appropriately trained professionals, the opportunity to participate in group sessions, and support from family members and others undertaking the exercise program), 7) The person's current fitness level and comorbidities (e.g. cardiovascular fitness may need to be improved before muscle-strengthening exercises are attempted, or a rehabilitation approach may be needed for people whose mobility is impeded), and 8) Initial weight gain is associated with muscle-strengthening exercises as muscles increase in size.

People who are making changes to their health behaviors may benefit from advice on ways to introduce and sustain increased physical activity. The following points are practical information to support weight management through physical activity. They can assist in identifying activities that are suitable and acceptable to the individual: 1) Ideas for increasing the amount of incidental activity (e.g. choosing the stairs, walking to do errands), 2) Ideas for low-impact/low-risk exercise options (e.g. brisk walking, swimming), 3) Ideas for exercising with others (e.g. bike riding with the children, joining a sports team), 4) Relative benefits of different types of exercise intensity (e.g. doing a vigorous activity in addition to regular moderate-intensity activity provides additional health benefits), 5) Practical ideas for maintaining motivation to exercise (e.g. starting with small changes in activity and avoiding situations that encourage long periods of sitting), 6) Suggestions for how to get involved in physical events and groups (e.g. joining local walking groups), 7) Advice on reducing sedentary activities (e.g. commuting by bicycle rather than car), and 8) Affordable approaches to physical activity (e.g. walking or jogging rather than joining a gym).

Supporting behavioral change: Education regarding weight loss and lifestyle change, including specific weight management strategies, can support behavioral change if it is combined with other interventions. Information may be delivered face to face, individually or within groups, and should be reinforced by resources (e.g., written, web-based, or audiovisual materials). Initial approaches include discussing techniques to support behavioral change, which can be supported in primary health care [71] [74] [81] [83] [149] [150] [151]. The following techniques (**Table 9**) can be used:

Psychological therapies: In the context of overweight and obesity, psychological therapies aim to assist individuals in making long-term changes to their lifestyle. A range of psychological interventions (e.g., behavioral therapy and cognitive-behavioral therapy) can facilitate weight loss and have been shown to have a more beneficial effect when combined with other lifestyle approaches. Individual or group-based psychological interventions may improve the success of weight management programs. Psychological and behavioral therapies should be

Table 9. Examples of techniques to support behavioral change.

Core strategies	Additional strategies
Goal setting	Assertiveness training
Self-monitoring of behavior and progress	Slowing the rate of eating
Stimulus control (e.g. recognizing and avoiding triggers that prompt unplanned eating)	Reinforcing changes
Cognitive restructuring (modifying unhelpful thoughts or thinking patterns)	Relapse prevention
Problem solving	

tailored to the individual, and his or her situation, such as: 1) Psychological therapies that can be delivered in primary health care by healthcare professionals trained in their use may significantly increase weight loss, and 2) More intensive psychological intervention may be required if a person has difficulty achieving behavioral change, or has mental health comorbidities and referral to mental health specialists with relevant expertise may be required [152].

Other supports for behavioral change: Lifestyle interventions can also be augmented by measures to reinforce behavioral aspects of care or provide incentives for adherence. Internet-based information and programs are increasingly popular. Delivery of evidence-based weight management programs via the internet should be considered part of a range of options for people with overweight and obese.

Effect of interventions to augment lifestyle interventions in adults: Internet-based information, goal setting, reminders, and text messages, in combination with internet lifestyle diaries or pedometers, are successfully used but not a replacement for face-to-face healthcare delivery. On using the financial rewards paid for the achievement of program goals, weight loss has remained the same, but the trend towards increasing effectiveness as the size of the reward increases [153] [154] [155] [156].

Complementary therapies and nutritional supplements: There is little evidence to support their use in assisting weight loss [157]-[165].

Intensive interventions:

Intensive interventions to support weight loss include very low-energy diets, weight-loss medication, and bariatric surgery. These may be considered as an adjunct to lifestyle approaches, especially when an adult: 1) has a BMI > 30 kg/m^2 or a BMI > 27 kg/m^2 with risk factors and/or comorbidities, 2) has been unsuccessful in reducing weight or preventing weight regain using lifestyle approaches. The choice of intervention will depend on the individual situation, including the urgency and aims of intervention, accessibility, and affordability.

For example, 1) The rapid weight loss associated with medically supervised very low-energy diets may encourage people to continue with a lifestyle change towards longer-term weight loss goals, reduce obesity-related comorbidities, and

may also be necessary when bariatric surgery is conditional on weight loss (e.g., prognosis after surgery is worse if BMI > 50 kg/m^2), 2) Weight loss medications may be helpful to both in producing initial weight loss and in preventing weight regain in longer-term management, 3) The significant weight loss associated with bariatric surgery provides improvements in some cardiovascular and metabolic risk factors, and type 2 diabetes. These interventions are likely to be used sequentially—for example, starting with a very low-energy diet to achieve weight loss, then using medications to help counter the hormone changes and increased hunger that follow weight loss. Bariatric surgery is not generally an immediate consideration unless other interventions have not been successful, other interventions are contraindicated, and a person's BMI is >50 kg/m^2.

New weight loss medications are being developed and trialed. In the future, combining a very low-energy diet followed by pharmacotherapy may be a reasonable alternative to bariatric surgical procedures. The role of primary health care in intensive weight management interventions depends on the severity of health risks and the expertise of the healthcare professional involved. Contraindications, adverse effects, treatment duration, and requirements for follow-up should be discussed with adults to ensure informed decision-making.

Very low-energy diets: Very low-energy diets involve replacing one or more meals each day with foods or formulas providing a specified number of kilojoules (e.g., 1675 - 3350 kilojoules). ***Meal replacements*** are defined as a single food or prepackaged selection of foods sold as a replacement for one or more daily meals but not as a total diet replacement. They are primarily protein-based and contain essential fatty acids, vitamins, and minerals but minimal carbohydrates. They reduce portion size and, consequently, energy intake. Health benefits of very low-energy diets include the motivating effect of rapid weight loss and a mild ketosis that may suppress hunger. Low-energy diets have been associated with weight loss, sleep apnoea improvements, and glycemic control in adults with type 2 diabetes. They are commonly used in medically supervised weight reduction programs for people with BMI > 30 kg/m^2 or >27 kg/m^2 with obesity-related comorbidities) or for whom rapid weight loss is necessary. Costs are associated with the use of very low-energy diets. Purchasing very low-energy diet items to replace meals may be costly for individuals, and their use requires frequent monitoring by healthcare professionals. The relevant healthcare professional to monitor use may be a GP, dietitian, or specialist nurse, depending on access to the type of provider [78] [79] [90] [166] [167].

Very low-energy diets are a helpful intensive medical therapy in supporting weight loss when used under medical supervision. Considering the individual situation, they may be a consideration in adults with BMI > 30 *kg/m^2 or with BMI* > 27 *kg/m^2 and obesity-related comorbidities.*

Contraindications for very low-energy diets: 1) Pregnancy or advanced age, 2) History of severe psychological disturbance, alcohol misuse or drug abuse, and 3) Porphyria, recent myocardial infarction, or unstable angina. A relative contraindication is insulin or hypoglycemic (except metformin), but it may be

used if medication dosage is adjusted appropriately [16] [17]. ***Adverse effects*** include cold intolerance, dry skin, hair loss, constipation, headaches, fatigue, and dizziness. Other potential effects are gallstones, increased serum uric acid levels and precipitation of gout, and reduced bone mineral density. Although restrictive eating has been strongly associated with the onset of binge eating, there is insufficient evidence of an association between medically supervised, very low-energy diets and new-onset eating disorders [167]. ***Treatment length*** varies but is usually 8 - 16 weeks**.** There is evidence that in specific obese individuals and under close medical supervision, very low-energy diets may be used safely for 12 months [167]. ***Careful monitoring*** of people on very low-energy diets is required. Tests to be carried out when beginning a very low-energy diet include liver function tests, lipid profile measurements, a complete blood count, iron studies, electrolytes, creatinine, and uric acid levels. Electrolyte and creatinine levels should be checked about six weeks after starting the diet or earlier if more careful monitoring is required (e.g., in people who have renal impairment or are using diuretics). A review of medications is also necessary (e.g., for people taking diabetes medication/insulin or warfarin). Psychological well-being should also be monitored during and after the very low-energy diet. There must be a nutrition education program and support for long-term weight management (e.g., delivered in primary health care or through referral to a dietitian) [167].

Discussion of very low-energy diets should cover: 1) Options in the food replacement regime (e.g. replace all three meals, or replace two meals and have one meal of protein, non-starchy vegetables and salad), 2) The need to select a nutritionally "complete product", 3) The importance of reading the instructions carefully, 4) The importance of achieving ketosis to suppress hunger and of testing for ketosis, 5) The importance of avoiding carbohydrate supplementation—non-starchy vegetables or protein can be eaten when hungry, 6) The need for a small quantity of fat each day (e.g. 1 tablespoon olive oil on salad or vegetables) to contract the gall bladder and prevent gallstones, 7) The need to drink when thirsty, 8) The need for fiber supplementation, 9) The need for follow-up by healthcare professionals during the period of the diet (about 12 weeks) and gradual weaning off the diet (over a period of around 8 weeks), 10) The fact that it is not necessary to achieve the goal weight with one period of diet use (there may be repeated periods of very low-energy diets separated by periods of weight maintenance), 11) Costs associated with very low-energy diets, and 12) The need for continuing weight maintenance program to reduce weight regain [166]. Written materials explaining the diet and supporting adherence (e.g., giving examples of carbohydrates) should also be provided.

Pharmacotherapy: weight loss medications

- The use of weight loss medications, in addition to lifestyle approaches, has been found to increase weight reduction in adults who are overweight or obese [107].
- We recommend adjunctive pharmacotherapy for weight loss and weight-loss maintenance for individuals with BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with

adiposity-related complications to support medical nutrition therapy, physical activity, and psychological interventions [168].

- There are three medications indicated for chronic obesity management in KSA in addition to health behavior changes: liraglutide 3.0 mg, naltrexone/bupropion in a combination tablet, and orlistat. All three medications have been shown to be effective in producing weight loss greater than placebo for duration of at least one year. Semaglutide also has been known for its weight reduction [169].
- Pharmacotherapy for weight loss can be used for individuals with BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with adiposity-related complications in conjunction with medical nutrition therapy, physical activity, and psychological interventions (liraglutide 3.0 mg, naltrexone/bupropion combination, orlistat and semaglutide [168].
- We recommend pharmacotherapy in conjunction with health behavior changes for people living with prediabetes and overweight or obese (BMI > 27 kg/m^2) to delay or prevent type 2 diabetes. (Liraglutide 3.0 mg); orlistat or semaglutide [168].

Orlistat: Orlistat is currently the only medication registered for use in treating overweight (with comorbidities) and obesity that has been evaluated for long-term safety. Health benefits Orlistat reduces the absorption of energy-dense fat by inhibiting pancreatic and gastric lipases. In conjunction with lifestyle intervention, orlistat: is associated with modest additional reductions in body weight in adults (2.6 - 3.7 kg) and slight reductions in systolic and diastolic blood pressure. It increases weight loss in adults with comorbidities, including metabolic syndrome, hypertension, and type 2 diabetes. It is associated with slight decreases in blood pressure, no adverse effects on lipid profile, and slight improvements in glycemic control in adults with type 2 diabetes. Cost-effectiveness studies of orlistat use show that it is not cost-effective for population-based outcomes, but other data suggest that it is more cost-effective in individuals who have numerous comorbidities (type 2 diabetes, hypertension, hypercholesterolemia) [66] [80] [84] [137] [170]-[175].

***Recommendation* 12:** *For adults with BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 and comorbidities, orlistat may be considered as an adjunct to lifestyle interventions, considering the individual situation. A*

Orlistat is contraindicated in pregnant or breastfeeding women and adults with malabsorption or hypersensitivity to orlistat. Reduced gallbladder function (e.g., after cholecystectomy) is a relative contraindication, and caution is advised when there is obstructed bile duct, impaired liver function, or pancreatic disease [176]. ***Adverse effects***: Gastrointestinal side effects are common with orlistat use and include: 1) Steatorrhea (oily, loose stools with excessive flatus due to unabsorbed fats reaching the large intestine), 2) Fatty fecal incontinence and 3) Frequent or urgent bowel movements. These effects can be controlled by adhering to a low-fat diet. Concentrations of fat-soluble vitamins (e.g., vitamins A, D, E, and K) are reduced with orlistat use. While they remain in the normal range,

supplementation may be required if long-term use is contemplated (supplement taken at night before bed). Orlistat interacts with some medications, and monitoring is required for people taking: Warfarin, as absorption of vitamin K, may be reduced, and the international normalized ratio (INR) increased. Fat-soluble immunosuppressive medications (e.g., cyclosporine), as absorption may be reduced. There is insufficient data regarding long-term orlistat use to determine its association with cardiovascular events and cardiovascular or all-cause mortality [66] [177] [178] [179] [180].

Treatment duration: Therapy with orlistat should be continued beyond 12 weeks only if at least 5% of initial body weight has been lost since starting medication. Therapy should be continued for as long as there are clinical benefits (e.g., preventing significant weight regain). Continuing risks and benefits should be discussed [38]. If the use of orlistat is considered, ***the discussion should cover***: 1) The fact that orlistat is not a substitute for a lifestyle change, 2) The need for continuous monitoring of the effect of treatment, and 3) The likelihood of weight being regained when medication is stopped. Information about dietary intake during treatment should also be provided. People who are considering taking orlistat should be advised that: 1) Taking orlistat results in gastrointestinal side effects if a low-fat diet is not followed, 2) The low intake of fat should be distributed over three main meals, and 3) Foods associated with an episode of diarrhea or fat leakage should be avoided—this will lead to a change towards the healthier dietary intake [178].

GLP1-RA: Liraglutide and semaglutide

GLP-1 agonism with current GLP-1 RA and emerging novel combined anti-obesity compounds represents a benchmark for future pharmacological anti-obesity treatment. The first drug for weight management approved by the Food and Drug Administration (FDA) and European Medicine Agency (EMA) is GLP-1 RA **liraglutide** 3.0 mg with once-daily administration [181].

The next-generation GLP-1 RA **semaglutide** 2.4 mg is the latest anti-obesity medication, approved by the FDA in June 2021. Compared with liraglutide, semaglutide has been subjected to some minor structural changes that resulted in greater efficacy and gained pharmacokinetic properties that allow once weekly dosing of semaglutide vs. once-daily administration of liraglutide [181] [182].

***Recommendation* 13:** *For obese adults with BMI* ≥ 30 *kg/m*^{2} *or more and with or without comorbidities, liraglutide* 3 *mg or semaglutide* 2.4 *mg can be used in addition to lifestyle interventions after considering the individual condition. A*

***Recommendation* 14:** *Certain precautions should be taken when prescribing GLP-RA* (*Liraglutide* 3 *mg or semaglutide* 2.4 *mg*): *Dose titration is needed and should be smooth.*

Counselling for gastrointestinal side effects. Discontinue if pancreatitis is suspected. For liraglutide, use caution in patients with kidney disease when initiating or increasing dose due to potential risk of acute kidney injury. A

Treatments for comorbidities with an effect on weight: Many medications

for treating other conditions have been found to affect weight (e.g., fluoxetine, topiramate, metformin, glucagon-like peptide agonists). These medications may also be beneficial for weight management when relevant comorbidities are present.

Bariatric surgery: Bariatric surgery (weight loss surgery) is an evolving subspecialty of gastrointestinal surgery. Various techniques are used to induce weight loss in people who have emphatically failed to achieve weight loss by other measures. Bariatric surgery aims to reduce intake by restricting gastric capacity and/or reducing the uptake by reducing exposure to the small bowel absorptive area. Procedures currently considered standard practice include the following: 1) ***Laparoscopic adjustable gastric banding*** (**LAGB**) involves placing a band around the stomach near its upper end to create a small pouch. This restricts the intake of food. The band can be tightened or loosened over time to change the extent of restriction. 2) ***Sleeve gastrectomy*** involves removing the more significant portion of the fundus and body of the stomach, reducing its volume from up to 2.5 L to about 200 mL. This procedure provides fixed restrictions and does not require adjustments like LAGB. 3) ***Roux-en-Y gastric bypass*** (**RYGB**) is a combination procedure in which a small stomach pouch is created to restrict food intake. The lower stomach, duodenum, and first portion of the jejunum are bypassed to produce modest malabsorption of nutrients and, thereby, kilojoule intake. 4) ***Biliopancreatic diversion*** is also a combination procedure involving removing the stomach's lower part and bypassing the duodenum and jejunum to produce significant malabsorption. This procedure tends to be performed in subspecialty centers. The choice of surgical technique is individualized and involves a discussion between the surgeon and the person. Newer procedures, including endoscopic techniques like ballooning and sleeving, are evolving. **The choice of procedure considers factors** such as age, access to services for follow-up and monitoring, preparedness to commit to frequent follow-up and continuing lifestyle interventions, previous interventions, and risk profile. For various reasons, different specialists offer some procedures but not others. There is consensus that better outcomes are achieved when a multidisciplinary team (e.g., including a bariatric physician, bariatric nurse, dietitian, exercise physiologist, and psychologist) is involved. Bariatric surgery is more effective than nonsurgical interventions. The degree of weight loss—approximately 20% - 30% of body weight in people with a BMI > 35 kg/m^2—is high. The type of surgery influences reductions in BMI in adults. They are greater after combination procedures (BMI reduction of 9.0 - 11.4 kg/m^2) than following purely restrictive procedures (BMI reduction of 2.4 - 10.1 kg/m^2). Weight loss trajectories over time also differ depending on the procedure. In the Swedish Obese Subjects (SOS) study, gastric bypass surgery produced the most significant long-term weight loss (25% ± 11%), followed by vertical banded gastroplasty (17% ± 11%) and fixed or variable banding procedures (13% ± 13%) [72] [75] [183]-[189].

Numerous studies have reported that bariatric surgery is a cost-effective weight

loss intervention compared with nonsurgical treatment. However, the variability in estimates of costs and outcomes is significant. Surgery has been shown to be a cost-effective option in people with newly diagnosed type 2 diabetes compared to those with established diabetes [101] [137] [189] [190]. Services for bariatric surgery and necessary follow-up may be more limited in rural and remote areas. The additional cost and resource implications for the individual and the health system include frequent follow-up and monitoring, transport issues in urban and rural areas, and accessibility to services and providers. The sustained lifestyle changes and additional intensive interventions that may be required to ensure the effectiveness of surgery should also be factored into individual and health system costs. Subsequent surgical procedures (for weight loss, complications, or cosmetic procedures) should also be considered a significant cost implication to the individual and health system.

***Recommendation* 15:** *For adults with BMI > 40 kg/m^2 or adults with BMI > 35 kg/m^2 and comorbidities that may improve with weight loss, bariatric surgery may be considered, considering the individual situation. A*

When indicated, bariatric surgery should be included as part of an overall clinical pathway for adult weight management delivered by a multidisciplinary team (including surgeons, dietitians, nurses, psychologists, and physicians) and includes planning for continuing follow-up.

Health benefits of bariatric surgery are significant short-term improvements in some cardiovascular and metabolic risk factors and short-term resolution of metabolic syndrome and newly developed (<2 years since diagnosis) type 2 diabetes. Data from long-term follow-up (*i.e.*, >10 years) suggest that most (but not all) health benefits are maintained in the long term [189]. It is associated with reductions in hypertension and lipid profiles. In the SOS study: 1) The incidence of high triglycerides was lower and the recovery rate greater among participants in the surgical arm after 2 and 10 years, 2) The incidence of low levels of high-density lipoprotein (HDL) (<2.17 mmol/L) was lower in the surgical group at two years but not after ten years, 3) There was no significant difference between groups in the incidence of elevated total cholesterol at either 2 or 10 years, 4) After ten years, participants in the SOS study who had gastric bypass had more significant reductions in triglycerides (28.0% vs. 18.0%) and total cholesterol (12.6% vs. 5.0%) and more significant increases in HDL levels (47.5% vs. 20.4%) compared to those who had gastric banding. The SOS study also found that compared with usual care, bariatric surgery was associated with a reduced number of cardiovascular deaths and a lower incidence of cardiovascular events in adults who were obese [101] [189] [191].

***Type 2 diabetes*:** There is growing evidence that bariatric surgery is a possible treatment for some people with type 2 diabetes. Studies have demonstrated improved glycemic control and medication use or the resolution of type 2 diabetes in many people who receive bariatric surgery**.** The International Diabetes Federation recommends consideration of bariatric surgery for people who have type 2 diabetes and a BMI > 35 kg/m^2 and for those with a BMI 30 - 35 kg/m^2 when an

optimal medical regimen cannot adequately control diabetes, especially in the presence of other cardiovascular disease risk factors. Bariatric surgery may be a consideration for people with a BMI > 30 kg/m^2 who have poorly controlled type 2 diabetes and are at increased cardiovascular risk, considering the individual situation. *The effect of surgery on glycemic control and resolution of type* 2 *diabetes varies with the stage of diabetes*, *bariatric procedure*, *and amount of weight lost*. For example: 1) Bariatric surgery (gastric bypass or biliopancreatic diversion) resulted in better glucose control at 2 years than conventional medical therapy, 2) 12 months of medical therapy plus bariatric surgery achieved glycemic control in significantly more obese adults with uncontrolled type 2 diabetes than medical therapy alone, 3) Sleeve gastrectomy in adults with type 2 diabetes improved glycemic control and comorbidities (sleep apnoea, hypertension, dyslipidemia) more than medical therapy, 4) Diabetes may be dramatically improved in adults with metabolic syndrome one year after bariatric surgery, but an adverse 90-day outcome is expected, 5) Improvements in HbA1c in mean blood glucose and insulin values at 10 years were more significant following gastric bypass than they are following gastric banding, 6) People with the shortest duration (<5 years) and the mildest form (diet-controlled) of type 2 diabetes had the greatest likelihood of resolution of diabetes, and 7) Resolution was more likely following procedures that combine restriction and malabsorption. *After the placement of an adjustable gastric band*, *improvements in glycemic control are dependent on weight loss*, and appreciable improvements in glycemic control may not be evident for some time. In contrast, people who receive RYGB may experience improved glycemic control before any weight loss occurs. When bariatric surgery results in the resolution of type 2 diabetes, it is unclear what the duration of effectiveness is or what monitoring, if any, should be performed for the recurrence of type 2 diabetes in people who have experienced disease resolution [72] [75] [189] [192]-[198].

The effect of bariatric surgery on long-term mortality is favorable, with lower rates of mortality among people who are obese who have had the surgery compared to those who have not had the surgery. However, some caution is needed in interpreting results as outcomes from the general medical community may not be equal to those of surgical centers of excellence. [67] [199] [200].

Indicators of abnormal renal function in adults with chronic kidney disease improve following bariatric surgery. There are generally improvements in symptoms of gastro-oesophageal reflux disease (GORD), although the nature of some surgical interventions can affect its resolution. There is some evidence that markers of liver function and inflammation improve in obese adults with diagnosed nonalcoholic steatohepatitis [86] [87] [91] [92] [200] [201].

Long-term weight loss: The mechanisms of long-term weight loss following bariatric surgery are yet to be determined. Evidence suggests that surgical manipulations (*i.e.*, the small gastric pouch with or without bypass of the duodenum and proximal jejunum) are insufficient to account for the resulting body weight loss alone. In fact, for some surgical procedures, post-operative changes in me-

tabolic profile have been shown to occur before losing weight. Changes in eating behavior and appetite may be more related to altered responses to gut hormones than the anatomical changes the surgery creates. Therefore, it is difficult to establish whether improvement in comorbid conditions with bariatric surgery is due to the weight loss or the changes in hormone balance, metabolism, pressure dynamics, and mechanics that each type of bariatric surgery produces [202] [203] [204] [205].

Suitability for surgery: Bariatric surgery in adults is most effective and safest in younger men with lower BMIs. Appropriate monitoring is required to maximize the safety and effectiveness of bariatric surgery in women, people older than 45 years, and those with higher BMIs. Bariatric surgery should not be performed during pregnancy [206].

Medical comorbidities: Medical contraindications include severe gastrointestinal disease, active cancer, unstable heart or lung disease, advanced liver disease with portal hypertension, uncontrolled obstructive sleep apnea with pulmonary hypertension, and severe blood or autoimmune disorders. While there are no contraindications, careful monitoring of people with hypertension and a high risk of pulmonary thromboembolism and diabetes is required [207].

Psychological comorbidities: The effectiveness of bariatric surgery does not appear to be influenced by the presence of depression or increased psychological dysfunction, dysfunctional eating behavior, binge-eating disorder, or a history of intervention for substance misuse. These comorbidities are, therefore, not considered absolute contraindications for surgery but should be assessed and treatment started before surgery where possible [208]-[217].

Ability to give informed consent: People must be able to give fully informed consent to bariatric surgery, so it may be contraindicated if the person is unable to understand the nature of the intervention and the need to commit to postoperative care plans.

Adverse events: While bariatric surgery can achieve long-term weight loss, the surgery is not always successful and may require revision or reversal of bariatric procedures depending on the type of surgery. Complications affect a significant proportion of people who have bariatric surgery. The Longitudinal Assessment of Bariatric Surgery 1 study 5 (n = 4776) reported rates of major complications at 30 days (4.1%) and mortality (0.3%) following primary bariatric surgery—death, serious complications, re-intervention or prolonged hospitalization were reported following LAGB (1.0%), laparoscopic gastric bypass (4.8%) and open gastric bypass (7.8%). A systematic review reported operative re-intervention (13%), laparoscopic revision (10%), port infection (2.6%), and acute cholecystitis (2.6%) as the main complications affecting people following LAGB. The SOS study reported perioperative complications (13%), pulmonary symptoms (6.2%), infection (2.1%), thromboembolism (0.8%), bleeding (0.9%), and operative death (0.25%) [183] [189] [218].

Discussing bariatric surgery: Information that should be highlighted in dis-

cussing bariatric surgery includes the types of procedure available, the associated health benefits and risks (e.g., adverse events), a reasonable period before surgery can take place, requirements before surgery (e.g., weight loss to reduce risk of adverse events, smoking cessation), follow-up requirements for the various procedures, cost of the procedure and follow-up care, potential for re-operation to be required at some stage, including the removal of the silicone band or the removal of the port with adjustable gastric banding, need for strict eating plans and physical activity regimes to be continued, need for lifelong vitamin and mineral supplementations to prevent nutritional deficiencies following procedures that reduce uptake, likelihood that some weight will eventually be regained, potential psychological effects of surgery, and need for continuing intervention to prevent additional weight gain.

***Follow-up post-surgery*:** Complications may occur following bariatric surgery and may differ depending on the type of procedure used. Appropriate assessment is, therefore, necessary regularly. If complications occur, they must be followed up by the appropriate specialist team or surgeon. The appropriate specialist team or surgeon should determine individual monitoring and follow-up protocols in consultation with the primary care health professionals involved. The role of primary care health professionals is to monitor the individual based on the specialist team or surgeon's advice, check on compliance where appropriate and refer as appropriate. Primary healthcare professionals have a continuing role in the care of people who have had bariatric surgery, including monitoring and treating comorbidities, including psychological distress and risk of suicide; continuing to promote the benefits of physical activity and healthy eating; assessing nutritional status, including for micronutrient and vitamin deficiencies that might develop over time, providing support for behavioral change (e.g., brief intervention, referral for psychological therapy), providing support for healthy nutrition (e.g., developing an eating plan or providing a referral to a dietitian) and sustained levels of physical activity (e.g., referral to an exercise program), and arranging reassessment and re-intervention as required (e.g., regular review of laparoscopic adjustable gastric bands by a bariatric clinician is necessary for the reassessment of the stability and integrity of the prosthesis) [219] [220] [221]. Eventual weight regains after bariatric surgery occurs regardless of the bariatric surgical type. Achieving long-term weight loss, therefore, requires weight management strategies to be continued after bariatric surgery has been performed. Also, the resolution of comorbidities may not be sustained in the longer term, and continuous monitoring of these is required.

Developing an appropriate weight management program:

When planning a weight management program with an individual, consideration is given to the person's age, weight history, background, comorbidities, and the costs and benefits of weight loss. It is also essential to consider the person's family, work, and social context.

Therapeutic engagement:

Weight loss and long-term weight management are challenging. Most people need continuing support to maintain their motivation to adhere to lifestyle changes and not "give up" if they lapse or relapse. While weight management is primarily each person's responsibility, healthcare professionals have a crucial role in suggesting strategies and providing continuing support. This is facilitated by a sustained relationship between one or more healthcare professionals and each person, which extends beyond individual consultations. Establishing an honest, respectful therapeutic relationship is significant in managing chronic, relapsing conditions that require long-term support. Such a relationship involves healthcare professionals building mutual knowledge, understanding, and trust, to maximize the potential for healing, empowerment, and beneficial change. Also, they need to be non-judgmental, patient, and empathetic and acknowledge the challenges people face, taking a collaborative approach that facilitates people being open about their particular situation, whatever their background or circumstances. In addition, discussing strategies and developing goals that people would like to work on in partnership, rather than imposing "solutions" on them, ensures that people continue to feel safe and supported, regardless of lapses and any changes in their circumstances.

Agreeing on treatment goals:

As behavioral change is fundamental to weight management, it may be a more appropriate short-term goal than weight loss, particularly for people who find weight loss difficult. Examples of behavioral change goals include reduced intake of energy-dense foods, regular eating (including breakfast), reduction in "non-hungry" eating (e.g., snacks), increased daily steps when walking, and increased days a week of planned physical activity. Specific tools may be of use in assisting people in identifying goals (e.g., SMART [specific, measurable, achievable, realistic, and timely]). Specific goals for individuals will depend on their situation but should be realistic and sustainable. For example, a person who is obese and has done no planned physical activity for some time may have a goal of a 5-minute walk each day in the first week and build up slowly from there. Treatment goals should also include health improvements (e.g., lowered blood pressure, blood lipids, and blood sugars), likely with only small amounts of weight loss. The increased benefit will be gained from further weight loss, particularly in people who are obese. Longer-term weight loss goals should be practical. A realistic estimate is around 5% - 10% of the initial weight. However, even after education about realistic weight loss, people may have high expectations about the weight loss they can achieve. It is essential to explain that even modest amounts of weight loss improve health and that weight gain and loss rates vary widely between individuals [222] [223] [224].

Tailoring lifestyle approaches to the individual:

All weight management programs will include lifestyle changes. Planning for lifestyle change needs to consider factors that may influence an individual's ability to change behaviors and his or her life stage. Availability and access also need to be considered when planning intensive interventions. Most individuals are

faced with challenges when attempting to change lifestyle behaviors (Tables 10-12).

Lifestyle interventions at specific life stages:

(A) ***Pregnancy*****:** Managing weight during pregnancy involves preventing excessive weight gain while maintaining adequate fetal nutrition. Women should be advised to moderate weight gain depending on their pre-pregnancy BMI (Table 13). Developing weight management plans with pregnant women while weight loss diets are contraindicated during pregnancy, dietary and exercise interventions in pregnancy can reduce maternal weight gain and improve outcomes for both mother and baby [225]. The 2009 US Institute of Medicine recommendations on weight gain in pregnancy are as follows: 1) Nutrition during

Table 10. Social factors that affect individual ability to change health behaviors.

Factor	Example of approach to providing support
Cultural factors affecting lifestyle choices and behaviors	Acknowledge the cultural significance of certain food and activities Ensure health messages are culturally appropriate and provide culturally specific resources
Limited access to healthy foods	Provide examples of affordable healthy food choices available locally
Limited understanding of high-energy versus low-energy foods	Provide practical nutrition messages (e.g. cut fat off meat before cooking, reduce sugar intake, increase consumption of fruit and vegetables, grill or boil foods rather than fry)
Limited opportunities for physical activity	Provide advice on increasing incidental activity and moderate-intensity activity (e.g. choosing the stairs, walking to work)
Attitudes to physical activity	Provide advice on locally available resources to support physical activity (e.g. walking groups, culturally appropriate physical activity classes, women-only venues)
Limited access to psychological services (e.g. due to costs or distance)	Consider alternative approaches to psychological support (e.g. telephone or online resources)
Limited access to culturally appropriate health services for follow-up	Involve relevant healthcare professionals to assist in providing culturally appropriate care (e.g. Aboriginal health worker, multicultural health worker, interpreter)
Limited access to healthcare services for follow-up (e.g. due to distance)	Consider referral to community-based program (peer support groups, commercial providers)
Lack of support to change	Involve family or close others in decision-making and interventions

Table 11. Physical factors that affect individual ability to make lifestyle changes.

Factor	Example of approach to providing support
Reduced fitness due to comorbidities	Promote the benefits of any improvements in fitness Provide advice on types of activity suitable to the individual's level of fitness Advise a gradual increase in activity as fitness improves Consider referral for management of comorbidities (e.g. to dietitian, sleep clinic), considering the individual situation
Reduced mobility (e.g. due to obesity or comorbidities)	Promote the benefits of any increase in activity Provide advice on types of activity suitable to the individual's level of mobility Consider referral to a physiotherapist or exercise physiologist
Physical disability	Consider severity of functional limitations, coexisting mental health characteristics and quality of social supports Consider involving relevant allied health professionals (e.g. exercise physiologist, physiotherapist, dietitian, social worker, occupational therapist)

Table 12. Psychological factors that affect individual ability to make lifestyle changes.

Factor	Example of approach to providing support
Past or current life stressors (e.g. abuse, trauma, grief)	Consider referral to a psychologist
Additional health behaviors that individual wishes to change (e.g. smoking, alcohol intake)	Provide resources to support other lifestyle changes (e.g. referral to quit services, drug and alcohol services) Consider referral to a psychologist
Mood disorders (e.g. depression)	Explore the ways in which mental health affects health behaviors (e.g. lack of motivation) and provide practical advice on enabling change (e.g. healthy foods that are simply prepared) Offer advice on community-based supports Consider referral to a psychologist
Eating disorders (e.g. bulimia nervosa)	Involve relevant healthcare professionals (e.g. psychologist, dietitian)
Serious mental illness (e.g. bipolar disorder, schizophrenia, psychosis)	Involve relevant healthcare professionals (e.g. psychiatrist, psychologist, dietitian)
Intellectual and developmental disability	Provide advice that is suitable to the individual's understanding Involve family and/or carers in discussions about lifestyle change Consider coexisting functional limitations Consider involving relevant healthcare professionals (e.g. dietitian, social worker)

Table 13. Weight gain depending on pre-pregnancy BMI.

BMI kg/m^2	25.0 - 29.9	30.0 - 34.9	35.0 - 39.9	≥40.0
Weight gain kg	6.8 - 11.3	5 - 9	5 - 9	5 - 9

pregnancy should be appropriate for good fetal development. 2) Low- to moderate-intensity physical activity during pregnancy is associated with various health benefits and is not associated with adverse outcomes. 3) Higher level activities may be possible for women involved in these before pregnancy who have the required fitness level. The intensity of activity should be reduced in the third trimester. 4) Lifestyle counseling may reduce maternal weight gain. 5) Very low-energy diets, weight loss medications, and bariatric surgery are contraindicated. 6) After pregnancy, extended breastfeeding is recommended. 7) Infants who are breastfed for at least six months are less likely to gain excessive weight and develop obesity later in life [225]-[240].

(B) ***Older people*****:** The approach to lifestyle intervention in older adults is debated, partly because of concern that weight loss could worsen frailty by accelerating the usual age-related loss of muscle. However, there is some evidence that the combination of weight loss and regular physical activity provides a more remarkable improvement in physical function and reduced frailty than either intervention alone. A recent analysis suggests that women may gain more benefits than men for the same level of physical activity and that being sedentary is especially harmful to older women [98] [241].

Developing weight management plans with older adults: 1) Multicomponent lifestyle interventions are likely to be the most successful. 2) Dietary advice should reflect evidence-based approaches for weight loss while emphasizing good nutrition. 3) Moderate physical activity is essential because it can reduce the risk of bone density loss and lessen other adverse health effects of being overweight and obese. 4) Physical activity should be tailored to accommodate chronic disease, sensory deficits, or functional limitations. 5) Innovative approaches may be needed to reduce barriers to lifestyle interventions in older adults (e.g., stigma, lack of evidence-based programs, and high costs of existing programs) [242].

There is insufficient data to evaluate the safety or efficacy of weight loss medication or bariatric surgery in older adults. Rates of adverse surgical outcomes found in younger adults may not be generalizable to older people because chronic disease increases with age, and both age and comorbidity are linked with perioperative risk**.** Limited observational data suggest that bariatric surgery can be safe in the short term in older adults [242] [243].

Supporting self-management:

A self-management approach may support lifestyle change and weight loss. Self-management approaches generally include lifestyle education, individualized approaches to care planning, and emphasis on defining the person's goals and suitability for people at different stages of change. Self-management techniques are part of a multicomponent intervention rather than a stand-alone in-

tervention. Examples of self-management approaches associated with weight loss in recent studies include peer-led education on improving self-efficacy in making changes, intensive weight loss counseling based on self-management principles, short-term goal setting or action planning, and an adapted "symptom cycle" [244] [245] [246] [247].

***Recommendation* 16:** *For adults, include a self-management approach in weight management programs. C*

Various healthcare professionals and organizations could deliver practical advice for self-management approaches. Resources such as Life scripts and other health promotion activities are readily available on the internet. Assistance with developing skills for self-advocacy and self-management requires support and consultation by healthcare or support programs for the individuals. This component may have time and cost implications. Group approaches are similarly practical to individual approaches and maybe a more cost-effective option for the healthcare system. Depending on local service providers and access to healthcare professionals, referral to community-based programs may be a cost-effective option for the individual and healthcare system to provide continuing self-management, lifestyle advice, and peer *support*. Self-monitoring of weight is a helpful self-management strategy—more frequent self-weighing is associated with more significant weight loss and weight gain prevention**.** Regular self-weighing (e.g., weekly) may be a valuable component of self-management [248] [249] [250].

Practical advice to support individual self-management:

Identify which changes to work on first. Start by making small changes and work up to your targets. Involve family and friends if appropriate. Identify activities and healthy foods that you enjoy. Monitor your progress (e.g. keep a food and/or exercise diary). Weigh yourself regularly (e.g. each week). Reward yourself for meeting each goal (e.g. spend time with a friend). Don't expect to meet all of your lifestyle change targets straight away.

Planning for review and monitoring:

The duration over which an intervention is provided and the frequency of contact with a health professional appear to influence the success of weight loss interventions in adults. Therefore, the weight loss program should include arrangements for regular review throughout initial weight loss and continuous monitoring for at least 12 months [62] [246] [251] [252] [253].

***Recommendation* 17:** *For active weight management in adults, arrange fortnightly review for the first* 3 *months and plan for continuing monitoring for at least* 12 *months, with additional intervention as required. B*

Increased frequency of contact may have resource implications for the health system and the individual. Depending on the level of obesity, comorbidities, and type of intervention, frequent monitoring can be undertaken by various healthcare professionals, organizations, or programs to reduce costs to the individual and healthcare system. Sustained weight loss is unlikely to result from episodic care but needs to be actively managed and monitored. Suppose the practice cannot provide a program in-house. In that case, referral to a group or estab-

lished weight loss program to provide ongoing monitoring, structured education, self-management, and peer support should be considered. Discussing cost and access considerations with the individual should include provider attendance and availability, transport, and suitability for specific activities based on age, life stage, and gender.

Referral:

Lifestyle interventions are well suited to delivery in primary health care. The role of primary health care in intensive weight loss interventions will depend on the severity of health risk (e.g., the degree of obesity and associated comorbidities), accessibility and cost, and the healthcare professional's availability and expertise in weight management. Referral may be appropriate in a range of situations (Table 14). However, while it might be ideal to refer in these situations, the primary healthcare professional may need to continue overall management if waiting times are extended, or specialist support is unavailable. Primary healthcare professionals should maintain a role in monitoring and reviewing progress, even when the person is referred for specialist care.

Primary healthcare professionals (e.g., practice nurse, social worker) may also need to assist people in addressing barriers to referral and attendance, including providing information about the cost of programs or attending visits to healthcare professionals, transport, attitudes towards treatment, and time of day that the program or provider is available.

Table 14. When to refer?

Referral to an allied health professional	Referral to specialist support
• When individuals ask for specific information related to weight management or indicate interest in undertaking a specific weight loss program • When community-based programs are available, especially for people with a BMI < 35 and without major comorbidities who are ready for change • When specific health indicators demonstrate increased health risks (e.g. increased blood pressure, lipid profiles, blood glucose) and the individual would benefit from interventions related to weight loss • When the individual's eating patterns are not meeting nutritional requirements (e.g. to a dietitian) • When the individual might benefit from attending a structured group support program When the individual is having difficulty achieving behavioral change and may benefit from a behavioral weight loss intervention (e.g. to a psychologist)	• When the individual has a BMI > 35 kg/m^2 or BMI > 30 kg/m^2 with comorbidities • When comorbidities need specialist management (e.g. musculoskeletal problems, sleep apnea, fertility problems, type 2 diabetes, eating disorders, depression or other mental health comorbidities) • When a very low-energy diet or weight management medication is recommended (e.g. refer to a specialist weight management clinic) • When bariatric surgery is a consideration (e.g. refer to a specialized bariatric surgery center) • When an endocrine or syndromic cause is suspected (e.g. refer to an endocrinologist)

6. Monitoring: Short-Term and Long-Term

Key messages

- A periodic review of the weight loss program in the first three months allows for assessing its suitability for the individual and supporting program goals.
- Long-term weight management is challenging—people need to overcome potent physiological responses that increase hunger, encourage weight to regain, and resist returning to weight-promoting lifestyle habits.
- As with weight loss, lifestyle interventions underpin long-term weight management, whether or not more intensive interventions are also used to help prevent or to reverse weight regain.
- Weight regain is common after weight loss. However, the health benefits of weight loss persist even if some weight is regained.
- Long-term monitoring and support are essential—longer-term approaches to supporting weight management that includes frequent contact with healthcare professionals achieve better results.
- Weight management may get easier over time. Once people have maintained a weight loss for 2 - 5 years, the chances of longer-term success significantly increase.

Review and monitoring: The early stages of the weight loss program provide an opportunity to establish a sustainable lifestyle change approach. Systematic review at this time may also support more rapid weight loss. Continuing review for 12 months and more aims to ensure that the weight loss program remains appropriate, comorbidities are monitored, and people are supported through the challenges associated with long-term weight management.

Early review of the suitability of the weight loss program: A weight loss program specific to the individual should achieve some weight loss in the first weeks of intervention. The early review includes assessing whether the person is facing challenges in keeping to the eating plan (e.g., whether the plan is suitable in terms of individual preferences and includes foods that are available and affordable), whether the type of physical activity being undertaken is suitable to the person's level of fitness and opportunities are available to increase physical activity (e.g., walking groups, community facilities), psychosocial support, including psychological therapy, is available and accessible, or any negative occurrences have resulted from the weight loss program (e.g., weight gain, worsening of comorbidities). This early review can be by a practice nurse, allied health professional, or community-based program leader and conducted individually or in a group.

The weight loss plan should be reviewed after 2 weeks to determine its suitability for that individual and to assess whether it needs to be modified.

Review in the first three months: Frequent (e.g., fortnightly) review should continue through the first three months of a weight loss program. A 3-month medical review may include calculating BMI and measuring waist circumference, and comparing these to baseline measurements and anticipated weight

loss and targets, tracking progress towards goals (e.g., whether health behaviors have changed), monitoring changes in risk factors and comorbidities, reviewing the care plan, providing support and encouragement. For adults who are overweight and have comorbidities or who are obese and do not lose weight in the initial stages of the weight loss program, additional intensive weight loss measures may be indicated, both for weight loss and to support motivation. Referral to healthcare professionals or services with expertise in obesity management should also be considered [152] [246] [251] [252] [253].

If there is no weight loss (less than 1% body weight or no change in waist circumference) after three months of active management, lifestyle behaviors and causes of weight gain should be reviewed. Intensive weight loss interventions may also be considered depending on the degree of overweight or obesity and whether comorbidities are present.

Continuing support: While contact with and support for the person may decrease after the first intensive 2 - 3 months, long-term monitoring and support are essential to weight management programs. The rate of weight loss can be expected to decrease or plateau after the initial stages due to physiological adaptation. The individual trying to lose weight may regard this as a failure of intervention because it can occur while they are still restricting energy intake and exercising regularly. Continuing support and encouragement are needed, including reiterating that even modest amounts of weight loss improve health and that weight gain and loss rates vary widely between individuals. Where people continue to have difficulty losing weight or maintaining a new lower weight, healthcare professionals should be aware of the possibility of psychological issues, including eating disorders. Continuing monitoring and support of weight management will also involve reviewing various health indicators (e.g., blood pressure, lipid profile) and managing the consequences and complications of overweight and obesity. Referral to allied health professionals or specialists may be appropriate in various situations [254].

Long-term weight management: When realistic treatment goals have been reached—for example, 5% of body weight lost or blood pressure lowered by a clinically significant amount—it is important to discuss strategies for managing weight in the longer term, including preventing weight regain. Weight regain is common after weight loss achieved by lifestyle interventions, with studies finding that 1) Weight loss is usually regained by five years of follow-up, 2) Weight regain to pre-intervention weight occurs regardless of whether the participant has overweight or class I, II or III obesity, and in participants with regular blood sugar, prediabetes and type 2 diabetes [100] [255] [256].

***Recommendation* 18:** *For adults who achieve initial weight loss, strongly recommend the adoption of specific strategies, appropriate to their individual situation, to minimize weight regain. A*

Weight regain is not caused simply by people resuming former lifestyle habits—instead, it has a solid physiological basis. The adaptation that causes slowing of weight reduction in the weight loss phase also causes weight to regain in

the longer term. The changes in energy balance regulation in the body that lead to reduced energy expenditure persist for at least one year [257]. Increasing evidence indicates that changes in appetite-regulating hormones also occur after diet-induced weight loss, including decreased levels of leptin, insulin, cholecystokinin, triiodothyronine (T3), and an increased level of ghrelin. Many of these changes would be expected to reduce feelings of fullness after eating (satiety) and increase hunger. Recent evidence suggests that hormone changes do not reverse for at least one year after initial weight loss [167] [258]. These findings indicate that, for successful long-term weight management, people must overcome strong physiological responses that encourage weight regain and resist a return to weight-promoting lifestyle habits.

Disordered eating patterns (including binge eating and strict dietary restriction), body dissatisfaction, inflexible thinking style, and eating to regulate mood or avoid negative affect are all associated with a greater likelihood of weight regain. People's social context, including their level of peer and family support, also influences their ability to manage their weight. Despite the evidence highlighting the challenges, there is evidence that long-term weight management is possible when specific strategies are identified and followed. There is also evidence that the health benefits of weight loss (e.g., preventing type 2 diabetes) are maintained in the longer term, even if there are some relapses [68] [146] [259] [260] [261] [262].

Factors influencing long-term weight management (Table 15): [263] [264] [265] [266]

Discussing long-term weight management

Preventing weight regain may be a more helpful focus than trying to lose more weight, as being satisfied with the amount of weight that has been lost supports long-term weight management. Also, even when weight management is successful, modest weight regains, and weight fluctuations are common. Acting rapidly is critical because of the difficulty of reversing even small weight regains. Clear messages are needed, so the individual understands that: 1) After weight loss, the body is "hardwired" to encourage weight to regain, so hunger may increase, 2) Preventing weight regain can be even more challenging than losing

Table 15. Barriers to and predictors of successful long-term weight management.

Barriers to successful long-term weight management	Predictors of successful long-term weight management
Physiological adaptation to energy deficit	Continued healthy eating plan
Waning motivation to sustain lifestyle change	High levels of regular physical activity
Resumption of old habits	Continued contact with health professional
Depressive symptoms	Self-monitoring of body weight
Negative peer and family influence	Peer and family support

weight, especially during the first year, 3) Weight regain is pervasive and is not a sign of failure, 4) Some benefits of weight loss persist even if a small amount of weight is subsequently regained, 5) It may be helpful to set a weight to regain limit at which advice from a healthcare professional is sought, and 6) If weight regain limit is attained, it is essential to continue to make sustainable lifestyle changes and possibly consider one or more intensive interventions [267] [268].

For long-term weight management, adults can be advised to act (e.g., seeing a healthcare professional) when small amounts of weight (approximately 3 kg) have been regained. If there is weight regain, consideration should be given to reassessing energy intake and physical activity and re-intervening with weight loss strategies.

Successful weight management strategies: An American national database of self-reported long-term weight management identified the following weight management strategies as being successful: 1) Maintaining high levels of physical activity and limiting sedentary activities (e.g., television viewing), 2) Eating a diet low in kilojoules, 3) Regularly eating breakfast, 4) Maintaining a consistent eating pattern throughout the week and year, 5) Identifying triggers of emotional eating and developing alternative strategies for regulating mood, 6) Frequently monitoring weight, and 7) Catching lapses before they become large-scale weight gains [146].

Some studies support the value of 200 - 300 minutes a week of physical activity to reduce weight gain after weight loss, and it appears that "more is better". While there is an overlap between weight loss and long-term weight management strategies, practices that lead to weight loss might differ from those that help people manage weight in the longer term [145].

In a cross-sectional survey of American adults who were successful at maintaining weight loss for one year, the following practices were associated with maintaining weight loss but not with initial weight loss: following a consistent exercise routine, rewarding themselves for keeping to their eating or physical activity plan, and reminding themselves why they need to control their weight. While most of these strategies involve self-management, healthcare professionals have an essential role in continued monitoring (e.g., through regular visits) to review weight and behaviors, provide continuing support, reinforce lifestyle and behavioral advice, and discuss intensive interventions when needed. Phone counseling and internet-based interventions can be used to augment long-term weight management [269] [270] [271] [272] [273].

Long-term weight management may be more successful if it involves a self-management approach, continuing contact with healthcare professionals and behavioral strategies for maintaining motivation. Self-management strategies for long-term weight management may include maintaining a healthy lifestyle, identifying ways to manage hunger, setting, and reviewing goals, and regular self-weighing.

Developing a long-term weight management program:

As with weight loss, the type and intensity of the long-term management pro-

gram will depend on various individual characteristics. Given the complex interaction of factors causing the weight to regain, the program should be sensitive to individual needs and differences and allow people to adopt behavioral changes that suit their lifestyles. Although the ideal outcome is stabilizing at the new lower weight, there may be other options. If this is the case, the aim should be to delay weight regain for as long as possible [264] [274].

Lifestyle interventions underpin long-term weight management, and for many people who regain weight, re-intervention with more intensive lifestyle changes is sufficient. Interventions to manage psychological issues may be required if the person has a mental health comorbidity (e.g., eating disorder, depression) or is continuing to find behavioral change difficult. Weight management may get easier over time. Once people have maintained a weight loss for 2 - 5 years, the chances of longer-term success significantly increase [275].

Very low-energy diets, pharmacotherapy, and bariatric surgery may be options where people cannot manage the increased hunger that follows weight loss and/or if obesity and/or comorbidities are causing health risks. Lifestyle interventions combined with pharmacotherapy result in less weight regain than lifestyle interventions alone. However, by ten years of follow-up, the most lost weight has been regained, regardless of whether weight was lost by lifestyle intervention or pharmacotherapy [76] [107] [171] [276] [277].

In people with Class III obesity, bariatric surgery is associated with less weight regain than lifestyle interventions or pharmacotherapy. Weight loss appears to be most significant in the first year after surgery but continues for 2 - 3 years. After this, weight regain appears to occur. However, at least 16% of weight loss can be maintained at up to 10 years of follow-up [72] [101] [188].

Long-term review and monitoring:

Studies involving long-term support have successfully prevented regain of baseline weight. Planning for review and monitoring should include discussion about: 1) the intensity of the program and schedule of visits, 2) the scope of self-monitoring and what will be reviewed at regular visits, and 3) the availability and benefits of participation in a weight management program in the community or person's workplace [265].

7. Obesity and Overweight Management Plan in DM

Obesity management is beneficial in the treatment of type 2 DM. For overweight or obese, modest and sustained weight loss improves glycemic control [34] [278] [279] [280].

Assessment: Each visit, **calculate BMI and document** it in the patient's medical record. Educate DM overweight or obese that higher BMIs increase the risk of CVD and all-cause mortality. Providers and patients should jointly determine goals and interventions to achieve weight loss [34] [278] [279] [280].

Interventions: Overweight or obese patients with type 2 DM should achieve and maintain > 5% weight loss. Diet, physical activity, and behavioral therapy

are interventions to reach this goal (Table 16). Plan to **achieve the target weight in 6 months**. Diets should be individualized with other interventions to achieve an energy deficit of 500 - 750 kcal/day. For those who achieved **weight-loss goals**, use long-term (1 year) comprehensive weight maintenance programs. At least once per month, contact them and encourage ongoing monitoring of body weight. **Short-term (3-month)** interventions with very-low-calorie diets (<800 kcal/day) and total meal replacements may be used with close medical monitoring. Long-term comprehensive weight-maintenance counseling is needed to maintain weight [34] [278] [279] [280].

Pharmacotherapy: Always minimize medications that cause weight gain to wither antihyperglycemic agents or other agents for comorbid conditions. Pharmacotherapy (Table 17) may be used for weight loss for selected patients with BMI ≥ 27 kg/m^2. Consider re-assessing pharmacotherapy after three months according to the effect on body weight [34] [278] [279] [280] (**Figure 2**).

Metabolic Surgery: People presenting for metabolic surgery should receive a comprehensive mental health assessment and support [34] [278] [279] [280].

Table 16. Treatment options for overweight and obesity in type 2 DM.

Intervention	BMI category (kg/m^2)				
	25.0 - 26.9	27.0 - 29.9	30.0 - 34.9	35.0 - 39.9	≥40.0
Diet, physical activity & counseling	+	+	+	+	+
Pharmacotherapy		+	+	+	+
Metabolic surgery			+/−	+/−	+

Table 17. Medications for the treatment of obesity in type 2 DM [34] [278] [279] [280].

Class	Relative weight loss	Side Effects	Therapeutic Considerations
Gastrointestinal lipase inhibitor: (orlistat)	↓	Loose stools, GI upset, rare liver failure	Oral medication, decreases fat absorption, may require vitamin supplementation
GLP-1 receptor agonist: (liraglutide 3.0 mg)	↓ ↓	Nausea, GI upset, rare gallstones and pancreatitis	Subcutaneous injectable, increases satiety

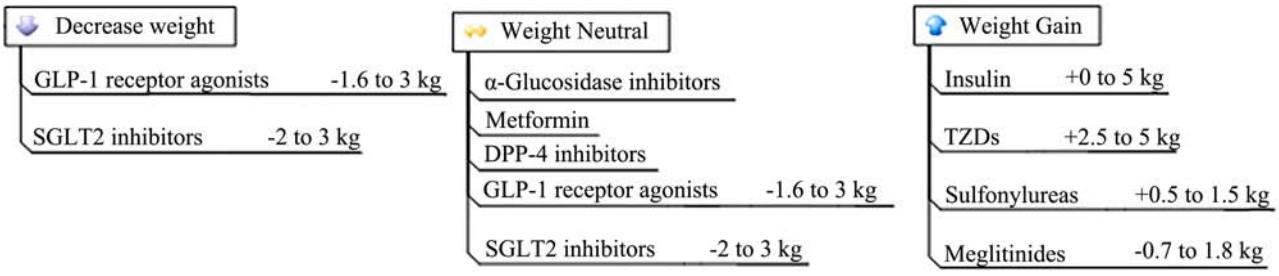

Figure 2. Weight effects of Antihyperglycemic drugs.

8. Conclusion

The early screening and management of obesity are beneficial against the significant burden, and always, prevention is better than treatment, so increase awareness of the public.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Clinical Practice Recommendations for Assessment and Management of Hypothyroidism

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Abstract

Hypothyroidism is a common disorder, potentially severe, often clinically ignored, easily diagnosed by laboratory tests, and highly treatable. It may cause chronic illnesses if left untreated. Saudi Society of Endocrinology and Metabolism (SSEM) assembled a panel of twelve endocrinologists with experience in thyroid diseases in adults and children and made up a task force. An initial concept proposal that included types of hypothyroidism, population, scope, and prevalence in Saudi Arabia was obtained. The proposal was divided into several topics discussed in February 2022. The panel approved that the consensus will include all types of hypothyroidism in Saudi Arabia, screening, diagnosis, management, and special population. A literature review was carried out. Most of the latest international guidelines were screened in Europe and USA. The literature search was completed in March 2022. They drafted a report that was distributed to the entire panel. Approval of the recommendations required consensus, defined as a majority approval. The recommendations were revised to accommodate any differences of opinion until a consensus was reached. Recommendations were finally formulated on April 2022. Subsequently, the panel reviewed and discussed the supporting rationale of

the revised recommendations. This article presents these practical recommendations.

Keywords

Hypothyroidism, Screening, Diagnosis, Management

1. Introduction

Hypothyroidism is a common disorder, potentially severe, often clinically ignored, easily diagnosed by laboratory tests, and highly treatable. It may cause chronic illnesses if left untreated. Most patients are oblivious to their condition as the symptoms of hypothyroidism are non-specific. It may be primary hypothyroidism due to damage in the thyroid gland or central due to pituitary gland disorder. It can affect many special populations, such as neonates, children, adults, pregnant women, and older people. Also, it can be subclinical hypothyroidism (mild or no symptoms) or overt hypothyroidism (clinically symptomatic) [1]. In Saudi Arabia, the prevalence of hypothyroidism ranged from 18.7% to 25.5%. Females represented 57.5% to 86.3% of cases [2] [3]. At the same time, congenital hypothyroidism among the Saudi population varied from 1:2666 to 1:4208 live births [4].

Saudi Society of Endocrinology and Metabolism (SSEM) assembled a panel of experts to develop a **consensus** that includes the screening, diagnosis, and management of different types of hypothyroidism in different populations.

2. Methods of Consensus Development

Twelve endocrinologists from the SSEM with more than 15 years' experience in thyroid diseases in adults and children made up a task force. An initial concept proposal that included types of hypothyroidism, population, scope, and prevalence in Saudi Arabia was obtained. The proposal was divided into several topics discussed in a hybrid physical and virtual meeting held on the 26th of February, 2022. The meeting panel approved that the consensus will include all types of hypothyroidism in Saudi Arabia (primary, central & subclinical), screening, diagnosis, management, and special population, and finally, among the entire Saudi population (nonpregnant and pregnant adults, childhood and adolescence and neonates).

Afterward, Expert writers searched the literature based on their search strategies, and they determined their databases. Most of the last updated government-sponsored guidelines were screened in the United States, Canada, and the United Kingdom. These included American Thyroid Association (ATA), Canadian Task Force on Preventive Health Care (CTFPHC), Choosing Wisely Canada, National Institute for Health and Care Excellence (NICE), British Thyroid Association (BTA), and European Thyroid Association (ETA). No attempt was

made to grade the rationale or recommendations. The literature search was completed in March 2022.

Draft reports written by the experts were then distributed electronically to the entire expert panel. Approval of the recommendations required consensus, defined as a majority approval. The recommendations were revised to accommodate any differences of opinion until a consensus was reached. Recommendations were finally formulated on April 2022. Subsequently, the panel reviewed and discussed the supporting rationale of the revised recommendations. Despite differences between the guidelines and the available drugs, the panel tried its best to develop a consensus statement to be valid worldwide.

3. Screening/Detection of Hyothiroidsim

3.1. Asymptomatic Hypothyroidism

Population-based screening has the potential for overdiagnosis, long-term monitoring, the need for follow-up testing, and consuming resources. The rationale is insufficient, and the benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults cannot be determined [5].

Recommendation 1: Population-based screening is **not recommended** for thyroid disease in asymptomatic nonpregnant adults.

3.2. Subjects for Screening

The American Thyroid Association and the American Association of Clinical Endocrinologists advise people over 60, those at higher risk for hypothyroidism, and expectant mothers to be screened for the condition [6]. The US Preventive Services Task Force identified several risk factors for hypothyroidism, including previous hyperthyroidism (which may have been caused by ablation therapy leading to iatrogenic thyroid dysfunction), female sex, advancing age, white race, type 1 diabetes, Down syndrome, family history of thyroid disease, goitre, and external-beam radiation in the head and neck region [1] [2].

Recommendation 2: Screen for hypothyroidism should be considered in patients older than 60 years, women older than 50 years.

Recommendation 3: Screen only those individuals (adults and children) with clinical risk factors for hypothyroidism.

Recommendation 4: High-risk patients for hypothyroidism are identified as patients with goiter, a history of autoimmune disease, previous radioactive iodine therapy and/or head and neck irradiation, Family history of thyroid disease, previous or current use of medications that may impair thyroid function, if there is a clinical suspicion of thyroid disease, type 1 diabetes, new-onset atrial fibrillation, or depression or unexplained anxiety.

3.3. Children

Out of a worldwide birth population of approximately 130 million infants annually, it is estimated that 37 million infants (29 percent) are screened, and ap-

proximately 12,000 infants with hypothyroidism are detected annually. Early detection and treatment of congenital hypothyroidism through screening prevents neurodevelopmental disability and optimizes developmental outcomes [7] [8].

TSH level elevation is widely noticed in obese patients, yet it is more likely to be one of the obesity sequels and commonly false hypothyroidism. Thyroid function test should only be performed in other healthy children only if they have short stature and diminished velocity relative to the puberty stage [9] [10] [11] [12].

Recommendation 5: Screening of all Saudi newborns is recommended with particular emphasis on those at risk of congenital hypothyroidism as preterm neonates; low birth weight and very low-birth-weight neonates; ill and preterm newborns admitted to neonatal intensive care units; and multiple births (particularly same-sex twins).

Recommendation 6: Avoid routinely measuring thyroid function and/or insulin levels in children with obesity.

3.4. Pregnant Women

The results of observational studies suggest that assessment of thyroid function only in women at high risk for thyroid or other autoimmune diseases (targeted screening) will miss up to one-third of women with subclinical or overt hypothyroidism (TSH > 3.5 mU/L) [13]. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association, recommended that patients who are planning pregnancy, including assisted reproduction, should be screened. At the same time, that universal screening is not recommended [13] [14] [15].

Recommendation 7: Screen for thyroid dysfunction in **all** asymptomatic pregnant women in the first trimester.

Recommendation 8: Screen for thyroid dysfunction in **all** women who are **planning for pregnancy**.

3.5. Screening Tests

Expert panels have agreed upon screening the general population using TSH only. The ATA recommends screening in all adults above 35 years and every five years after that. The AACE recommends routine TSH level testing in older patients (ages not specified), especially women. The American Academy of Family Physicians suggests routine screening in asymptomatic patients older than age 60 years, and the American College of Physicians recommends case finding in women older than 50 years [16] [17] [18] [19].

Recommendation 9: Order TSH only for **all** patients, and if abnormal, TSH measurement should be repeated along with additional evaluation or treatment depending on the findings:

If the TSH is above the reference range, measure free T4 in the same sample.

If the TSH is below the reference range, measure free T4 and free T3 in the same sample.

Serum concentrations of Anti-Thyroid Peroxidase Antibodies (TPO-Ab) are increased in more than 90% of patients, as almost all of them have autoimmune thyroiditis [20].

Recommendation 10: Do not routinely test for TPO-Ab.

The American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) recommend measuring TSH in any high-risk people for hypothyroidism (e.g., personal history of type 1 diabetes or other autoimmune diseases, family history of thyroid disease, history of neck radiation to the thyroid, history of thyroid surgery) [7].

Recommendation 11: Order TSH at initial screening for **some** patients recommended for screening.

Recommendation 12: Order TSH, T4, and anti-TPO at initial screening for **some** patients recommended for screening if thyroiditis is suspected.

Routine screening is required for all neonates to detect primary hypothyroidism. An increase in TSH concentration can last up to 24 h following birth. Thus, it is best to measure a sample taken at least 48 h after delivery to avoid false positive results. Newborn babies should be screened for congenital hypothyroidism by measurement of bloodspot TSH using a sample collected within 2 - 8 days after birth as part of a national screening program. All hypothyroid neonates should be treated as early as possible.

Recommendation 13: For newborn screening, it is recommended to use a primary TSH/backup T4 method TSH. The sample is to be collected within 2 - 8 days after birth.

3.6. Screening Interval

Due to these problems, many qualified experts advise repeating thyroid function tests if the results are above or below a stated reference interval for confirmation of persistent dysfunction (for instance, over 3- to 6-month intervals in asymptomatic individuals), before making a diagnosis or thinking about any treatment options, unless the serum TSH level is higher than 10.0 or lower than 0.1 mU/L. In four to six weeks, the patient should have another evaluation and check their serum TSH levels. The patient will need another TSH measurement in six weeks if the TSH remains over the reference range [21] [22] [23].

Recommendation 14: Do not repeat thyroid function tests if TSH is normal except for diabetes patients.

Recommendation 15: Repeat thyroid function tests if TSH is abnormal in asymptomatic persons. The optimal screening interval for thyroid dysfunction is 4 - 8 weeks.

Recommendation 16: Repeating the tests for thyroid dysfunction if symptoms worsen or new symptoms develop but not sooner than **six** weeks from the most recent test.

4. Diagnosis of Hypothyroidism

In populations who have been screened, the accuracy of hypothyroidism diagnosis based on clinical findings is quite low. In a case-control study, 30% of newly hypothyroid patients reported symptoms, whereas 17% of controls with normal thyroid function reported the same nonspecific symptoms. Clinical diagnosis errors and inaccuracies of hypothyroidism may be connected to other medical and non-medical diseases with comparable symptoms [24].

Recommendation 17: Generally, hypothyroidism diagnoses rely on thyroid function tests because of the lack of specificity of the typical clinical manifestations.

4.1. Primary Hypothyroidism

Hypothyroidism is diagnosed when there is a subnormal serum free T4, either primary, where serum TSH is elevated, or central, where serum TSH is normal or low. There is controversy about the upper limit of normal serum TSH. The majority of laboratories have been using 4.5 to 5.0 mU/L values. The National Academy of Clinical Biochemistry recommended that the upper limit of normal euthyroid is 2.5 mU/L because 95% of euthyroid volunteers had serum levels within this limit when screened [25] [26] [27] [28].

The upper limit of TSH values may elevate with age, as seen in the NHANES (National Health and Nutrition Examination Survey) III population. If the TSH upper level stays at 4.5 mU/L, 74% of the TSH values of elderly patients older than or equal to 80 years without TPO-Ab positive values would be above this level. According to a reanalysis of the NHANES III TSH distribution curves in TPO-Ab negative individuals between 50 - 59 years, TSH upper levels would correspond to 4.2 mU/L, between 60 - 69 years, to 4.7 mU/L, between 70 - 79 years, to 5.6 mU/L, and in subjects over age 80, to 6.3 mU/L [29].

Previous literature showed that positive results of TPO-Ab tests had a significant association with hypothyroidism. Elevated TPO-Abs titers in subclinical hypothyroid patients signify progression prediction to overt hypothyroidism. Many societies and clinical Endocrinologists support TPO-Abs measuring in patients with subclinical hypothyroidism because TPO-Abs were positive in patients with a high risk of developing hypothyroidism [30] [31] [32].

Recommendation 18: Laboratory findings in **primary hypothyroidism** include a decrease in serum free thyroxine (FT4) and an increase in serum thyroid stimulating hormone (TSH).

Recommendation 19: An elevated serum TSH in **primary hypothyroidism** is above the normal reference range's upper limit, typically 4 - 5 mU/L and 2.5 - 3 mU/L in healthy individuals without thyroid disease.

Recommendation 20: Serum TSH distribution shifts towards higher values with age > 70 or obesity: 6 - 8 mU/L in healthy octogenarians (between 80 and 89 years old), 4.6 mU/L in persons older than 70 - 80 years, and up to 7.5 mU/L in class 3 obesity.

Recommendation 21: Measure TPO-Abs in:

- Adults with TSH levels above the reference range but do not repeat TPO Abs testing in primary and subclinical hypothyroidism.
- Children and young people with TSH levels above the reference range, with possible repeat TPO Abs testing at the time of transition to adult services.

4.2. Secondary Hypothyroidism

Weight gain and intolerance to cold complaints are the most common. Symptoms of concomitant hormone deficiencies, such as hypogonadism could mask the clinical manifestations of central hypothyroidism. Thus, laboratory testing is crucial for those patients. Central hypothyroidism is diagnosed with a decline in serum free T4, despite a low or normal TSH in the same laboratory testing [33] [34] [35] [36].

Hypothalamus or pituitary disorders cause thyroid hormone deficiency, defined as central hypothyroidism, resulting in normal or low TSH levels with decreased free T3 and T4. One study showed that in central hypothyroidism, free T4 was low normal in 18% of adult patients, where the rest were below normal levels, while the majority had normal levels of TSH. Normal levels of TSH are due to its normal immunoactivity, yet its biological activity is diminished. Measurement of T3 levels is rarely necessary for the diagnosis of central hypothyroidism. This recommendation is based on ETA Guidelines on the Diagnosis and Management of Central Hypothyroidism [19] [37] [38] [39] [40].

Recommendation 22: The diagnosis of central hypothyroidism is based on clinical manifestations and thyroid function tests.

Recommendation 23: Laboratory findings in **secondary (central) hypothyroidism** as normal or low level of TSH in the presence of decreased serum free T4.

Recommendation 24: Measure serum TSH and free T4 if pituitary or hypothalamic disease is suspected (e.g., a young woman with amenorrhea and fatigue).

Recommendation 25: Measure free T4 if the patient has convincing symptoms of hypothyroidism despite a normal TSH result.

Recommendation 26: It is not helpful to measure T3 in most patients with suspected central hypothyroidism. Although, it may aid when the diagnosis of central hypothyroidism is uncertain.

4.3. Diagnosis during Pregnancy

High TSH and low free T4 characterize overt hypothyroidism. Two factors donate to this result: hypothyroid women with no ovulation and newly diagnosed or undertreated hypothyroidism. Spontaneous abortion in the first trimester is observed in this type of pregnancy [41] [42] [43]. Concerning reported studies, representing the guidelines published by the American Thyroid Association or the American Endocrine Society suggested the following TSH reference range: first trimester, 0.1 to 2.5 mU/L; second trimester, 0.2 to 3.0 mU/L; third trimes-

ter, 0.3 to 3.0 - 3.5 mU/L [44] [45] [46] [47] [48].

Trimester-specific reference range of thyroid function might vary a lot. It affects the accurate diagnosis, causing delays or undertreated conditions. Guidelines released by the American Thyroid Association for the Diagnosis and Management of Thyroid Disease in 2017 recommended that trimester-specific thyroid function reference ranges were crucial in various laboratories and regions to detect and control pregnancy thyroid disorder more appropriately [49].

There has been a strong debate about the importance of hypothyroidism, represented by high TSH and hypothyroxinaemia (low FT4), as the more prognostic of events in pregnancy. This hypothesis found support by Dutch studies, which showed an association between euthyroid hypothyroxinaemia and delayed cognitive development at different ages. Total T4 assay is preferred to free T4, especially in the last part of pregnancy. American Thyroid Association, European Thyroid Association, and Endocrine Society guidelines state that TT4 elevates 1.5 times pre-pregnant levels after week 16 of pregnancy [50]-[55].

Recommendation 27: Overt hypothyroidism is defined as an elevated TSH concentration in conjunction with a decreased free T4 concentration which is population and trimester specific.

Recommendation 28: If there is a generalized trimester-specific reference range, it will be as follows: 0.1 - 2.5 mU/L for the first trimester, 0.2 - 3.0 mU/L for the second trimester, and 0.3 - 3.0 mU/L for the third trimester.

Recommendation 29: When possible, population-based trimester-specific reference ranges for serum TSH should be defined through assessment of local population data representative of a health care provider's practice.

Recommendation 30: When evaluating thyroid tests during pregnancy, we typically measure TSH and free T4.

Recommendation 31: Measurement of total T4 may be superior to free T4.

4.4. Congenital Hypothyroidism

High TSH and low free T4 results on serum testing indicate primary hypothyroidism. Treatment is indicated, starting as soon as possible. High TSH and normal free T4 or total T4 results on serum testing indicate subclinical hypothyroidism. Treatment should be initiated if the TSH is highly elevated (e.g., >20 mU/L). If the serum FT4 is low and TSH is low, normal, or slightly elevated, the diagnosis of central congenital hypothyroidism should be deemed. In most countries, there are newborn screening programs, and infants with congenital hypothyroidism are diagnosed after detection by screening tests. The diagnosis should be endorsed by finding an elevated serum TSH and low T4 or free T4 level. Other diagnostic tests, such as thyroid radionuclide uptake and scan, thyroid sonography, or serum thyroglobulin, may help spot the underlying causes [56] [57] [58].

Recommendation 32: The diagnosis of hypothyroidism can be confirmed or excluded by the results of serum tests of thyroid function.

Recommendation 33: If the diagnosis of hypothyroidism is confirmed, other studies (such as thyroid radionuclide uptake and scan, ultrasonography, serum

thyroglobulin, tests for thyroid autoantibodies, or urinary iodine excretion) may be performed to identify the cause.

Recommendation 34: In congenital hypothyroidism: High TSH and low free T4 confirm the diagnosis of primary hypothyroidism; High TSH and normal free T4 or total T4 defines subclinical hypothyroidism; and Low or normal TSH, low free T4 suggests the possibility of central hypothyroidism.

5. Management of Hypothyroidism

5.1. Managing Primary Hypothyroidism

5.1.1. Levothyroxine Replacement Therapy

Levothyroxine (LT4) is the cornerstone for the treatment of hypothyroidism. Oral LT4 has a prolonged serum half-life that allows daily administration and results in the remission of the signs and symptoms in most patients. Thyroid hormone action is crucial for growth and is critical in adults' function regulation and organ system metabolism. LT4 is converted peripherally into its active metabolite T3 [59] [60] [61] [62].

Recommendation 35: Levothyroxine is the standard replacement therapy for correcting primary hypothyroidism in adults, children, and young people. That is because of its long-term efficacy, safety profile, ease of administration, and low cost.

5.1.2. New Formulation of Levothyroxine Therapy

Most patients use LT4 tablets. One study reported that the pharmacokinetic characteristics of the gel capsule were the same as tablets in healthy individuals. The gel capsule or liquid is an option for patients with suspected poor absorption of the standard solid tablet, especially in the presence of atrophic gastritis. It may also be better absorbed after bariatric surgery [63].

Recommendation 36: Using levothyroxine (LT4) dissolved in glycerin and supplied in gelatin capsules or liquid formulation has no advantage over tablets. The soft gel capsule/liquid may be an option for patients with suspected poor absorption of the standard solid tablet. Also, it may be an option with the concomitant use of proton pump inhibitors or coffee. It may also be an option after bariatric surgery. Increasing the dose of levothyroxine tablet with monitoring of TSH is a less costly option than new formulations.

5.1.3. Switching between Formulations or From Brand to Generic

The bioequivalence of different LT4 formulations is controversial. Alteration in the LT4 content of brand-name and generic names guided many professionals to prefer a particular formulation. In 1997, a study of two generic formulations and two brand names of LT4, using US Food and Drug Administration (FDA)-recommended methodology to determine bioequivalence, stated that the four preparations were equivalent. Nevertheless, some experts considered the methodology used to determine bioequivalence in the study imperfect since endogenous T4 concentrations were not considered [64] [65] [66].

Due to the narrow therapeutic index of LT4, FDA has stipulated that LT4 formulations maintain 95% - 105% of their stated potency, amended from a prior requirement of 90% - 110%, during their shelf life. Moreover, FDA has required that all LT4 products be reassessed as if they were new drugs. America Thyroid Association advises maintenance of a specific formulation of LT4. Switches between LT4 products could potentially cause alterations in the administered dose and should largely be avoided for that reason [59] [67].

Recommendation 37: We recommend that patients remain on the same formulation used of levothyroxine.

Recommendation 38: It is acceptable to take either a generic or a brand-name formulation. Switching levothyroxine formulations (from brand to generics or different brands from different countries) has to be made cautiously and then re-evaluate the serum TSH until it is at a steady state.

5.1.4. Dosing and Administration

Starting dose based on the serum level of TSH, with a full replacement dose (1.6 μg/kg), is required when the serum TSH is significantly elevated, and lower doses (e.g., 25 - 50 μg) are required in mild hypothyroidism. T4 requirements relate better with lean body mass than total body weight. In one study, the average full replacement dose after thyroidectomy was 1.76 mcg/kg body weight for body mass index (BMI) < 25 kg/m^2, 1.47 mcg/kg for BMI 25 to 29 kg/m^2, 1.42 mcg/kg for BMI 30 to 34 kg/m^2, 1.27 mcg/kg for BMI 35 to 39 kg/m^2, and 1.28 mcg/kg for BMI over 40 kg/m^2. Patients who can wait an entire hour before eating breakfast are few. The closeness to food intake, instead of any time of day, is more critical. A meta-analysis showed no significant difference in the effectiveness of morning dosing compared to bedtime dosing based on TSH level assay [7] [68] [69] [70].

Some studies showed that TSH levels were lower and constant in the case of fasting administration of LT4 than with the non-fasting administration (e.g., mean serum TSH 1.06 ± 1.23, 2.93 ± 3.29, and 2.19 ± 2.66 mU/L if administered one hour before breakfast, with breakfast, or two hours after the last meal at bedtime, respectively) [71] [72].

Recommendation 39: For adults < 65 years old: start levothyroxine at 1.6 mcg/kg body weight per day (rounded to the nearest 25 mcg) with no history of cardiovascular disease.

Recommendation 40: Dosing should be adjusted based on actual body weight and ideal body weight.

Recommendation 41: Regarding administration concerning meals, we recommend that levothyroxine be consistently taken either 1 hour before breakfast or at bedtime after ≥3 hours of the evening meal for optimal, consistent absorption.

5.1.5. Target Therapy

The aim is to maintain serum TSH levels within the normal range (0.5 to 5.0 mU/L). Nevertheless, there is an age-related variation where higher TSH con-

centrations were measured in elderly patients. Amongst patients with goiter, nearly 50 percent will experience a decrease in goiter size, which delays the fall in TSH secretion. The appropriate upper limit of normal for serum TSH is controversial. The serum TSH is the parameter used to adjust the LT4 dose, with the target TSH typically being 0.5 to 3.5 or 4 mU/L [7] [73] [74] [75].

Recommendation 42: The goals of therapy for levothyroxine therapy are normalization of serum TSH, resolution of symptoms and avoidance of overtreatment.

Recommendation 43: We recommend maintaining TSH levels within the normal reference range when treating primary hypothyroidism with levothyroxine. Target normal range is 0.5 to 4.0 mU/L.

5.1.6. Monitoring and Assessing Adequacy of Therapy

In agreement with the most recent guidelines published by the ATA, "TSH is the most dependable marker of competence of replacement treatment, and a level within the reference range (0.4 - 4.0 mU/L) is to be the therapeutic target." As recommended by NICE guidelines for treating hypothyroidism, they agreed that TSH levels could take up to 6 months to return to the reference range if they have been very high or have been high for a long time. They agreed that healthcare professionals should consider this when adjusting doses to avoid large dose increases that could cause thyrotoxicosis. They made different recommendations for children under two years because of the impact of poorly treated hypothyroidism [7] [76].

Recommendation 44: TSH is the recommended marker for adequacy of levothyroxine therapy. Do not use Free T4 or T3, or clinical symptoms to monitor and adjust levothyroxine therapy.

Recommendation 45: For adults, measure TSH every 3 months until the level be stabilized (Two similar measurements within the reference range three months apart), and then once a year.

For children aged 2 years and over and young people, measure Free T4 and TSH every 6 - 12 weeks until the TSH level be stabilized (Two similar measurements within the reference range three months apart), then every 4 - 6 months until after puberty, then once a year.

For children aged between 28 days and 2 years, measure Free T4 and TSH every 4 - 8 weeks until the TSH level be stabilized (Two similar measurements within the reference range two months apart), then every 2 - 3 months during the first year of life, and every 3 - 4 months during the second year of life.

5.1.7. Factors Affecting Dose Required, Concomitant Medications, Concomitant GIT Condition

Levothyroxine dosing is affected by body weight. Studies have shown that patients demonstrated an alteration in levothyroxine requirement after weight loss bariatric surgery. Up-titration of the levothyroxine dose when there is weight gain is a recommendation of the Guidelines on the Diagnosis and Management of Central Hypothyroidism [35] [77] [78].

Carbamazepine, phenobarbital, rifampin, and phenytoin can increase the levels of the LT4 glucuronidation enzyme. Goldberg *et al.* mentioned an example, "the concurrent administration of rifampin and LT4 was correlated to a significantly higher area under the plasma T4 concentration-time curve" [79] [80] [81].

In a prospective study, the cure of *H. pylori* was linked with serum TSH levels reduction from 30.5 to 4.2 mU/L in nonresponsive patients to high doses of LT4. Moreover, eradication of *H. pylori* and starting omeprazole were correlated with low and high TSH values, respectively. Furthermore, in patients who took LT4 therapy, the degree of their LT4 requirement was associated with the existence or nonexistence of serum parietal cell antibodies. Celiac disease is likewise more common in patients with underlying Autoimmune thyroid disease. Two retrospective studies recorded higher LT4 needs in patients with celiac disease compared with unaffected hypothyroid patients [82] [83] [84] [85].

Recommendation 46: Levothyroxine doses should be increased if weight gain/loss is increased or decreased by more than 10% of body weight.

Recommendation 47: Measure TSH levels when medications such as phenobarbital, phenytoin, carbamazepine, rifampin, and sertraline are initiated as high doses may be required.

Recommendation 48: Evaluation of gastrointestinal disorders such as H. pylori-related gastritis, atrophic gastritis, or celiac disease should be considered, as levothyroxine dose requirements are much higher than expected. If such disorders are detected and effectively treated, re-evaluation of TSH and levothyroxine dosage is recommended.

5.1.8. Failure of Therapy

Patients with gastritis have higher requirements for LT4. A study showed that the LT4 dose was higher in patients with parietal cell antibodies. The same consequence can be seen in celiac disease patients [83] [84].

In patients with elevated TSH, it should be established that LT4 is taken daily with water on an empty stomach, before breakfast for an hour, and any medicines that affect T4 absorption should be taken several hours after the LT4 dose. Poor compliance is the most popular explanation for high LT4 dose requirements. Patients will admit to occasionally forgetting their tablets. Nevertheless, it is hard to determine how often "occasionally" happens. Clinicians can check adherence by direct patient reports, clinical improvement, or pharmacy refills. A study also suggests checking for proper storage of LT4 tablets (e.g., moisture, light protection, and temperature) [86] [87] [88].

Dose adjustment of LT4 is regularly required regardless of the initial dose estimate. This happens because of many factors, including limitations in the dose calculations, inter-patient differences, drug absorption, or concurrent diseases or medications [59].

The half-life of levothyroxine is nearly one week. If needed, reexamining thyroid condition by measuring TSH levels and free thyroxine levels are required after six weeks of treatment. If the TSH is not at the preferred goal, the LT4 dose

can be modified. In a systematic review that included nine randomized trials, one trial stated the advantageous effects of combination therapy on feelings, quality of life, and psychological functioning compared to LT4 therapy alone. The following meta-analysis of 11 randomized trials included 1216 patients revealed that there was no advantage of combined therapy [68] [89] [90].

Recommendation 49: If TSH elevation persists, adherence to therapy, proper administration regarding food, other co-medications, or diseases should be checked.

Recommendation 50: If symptoms persist, adjust the levothyroxine dose to achieve optimal well-being without reaching thyrotoxicosis.

Recommendation 51: If symptoms persist despite a normal serum TSH level, we recommend measuring free T4 with TSH in patients with hypothyroidism symptoms to exclude other causes.

Furthermore, acknowledgment of the patient's symptoms and evaluation for alternative causes are recommended in such cases. Future research into whether there are specific subgroups of the population being treated for hypothyroidism who might benefit from combination therapy should be encouraged.

5.1.9. Special Treatment Situations: (Target)

Coronary heart disease: The thyroid hormone raises myocardial oxygen requirement, correlated to a small risk of arrhythmias, angina, or myocardial infarction in older patients. A total of 1961 reports are the most prominent and finest study of the impacts of starting thyroid hormone on chest pain in patients with hypothyroidism. Among 1503 hypothyroid patients, fifty-five patients had angina before the replacement therapy. Through therapy, 21 improved, 25 had no difference, and 9 had more angina. While thirty-five patients experienced new angina during treatment, 6 in the first month, 6 in the first year, and 23 after one year. Hence, angina may improve with LT4 treatment, and it does not often first appear during LT4 replacement therapy [91] [92].

Recommendation 52: For patients with cardiovascular disease: start levothyroxine at a dosage of 12.5 - 25 mcg/day with *slow titration* over 4 - 6 weeks based on symptoms and serum TSH levels.

Elderly patients: Patients older than 60, with concomitant cardiovascular problems, or patients with a history of coronary heart disease should start treatment with 25 to 50 mcg LT4. The dose can be raised by 12 to 25 mcg/day every three to six weeks to achieve complete replacement, as determined by a normal serum TSH. However, if the increase in dose results in cardiac symptoms, in this case, less than a full replacement can be accepted. It is crucial to note that there is an age-related turn towards higher TSH concentrations in older patients, with an upper limit of normal of nearly 7.5 mU/L in 80 years old [93].

Recommendation 53: Patients over 65 - 70 years should start levothyroxine at lower doses (25 - 50 mcg/day) with titration based on TSH level for adults with a history of cardiovascular disease.

Infants and children: Delays in diagnosis and treatment of hypothyroidism

in infants lead to neurocognitive impairment. However, the intelligence quotient (IQ) and neurologic development may endure after diagnosis if the infant has suboptimal treatment throughout the first two to three years of life, a time when the thyroid hormone is crucial for normal brain development. Hence, proper initial therapy and follow-up are vital to ensure optimum dosing of thyroid hormone, with monitoring and dose adjustments and support for the family to promote close obedience to treatment. The quick normalization of thyroid hormone levels (In the first two weeks after therapy initiation) and the maintenance of somewhat higher FT4 concentrations during the first year of life results in a better outcome. The regular monitoring of TSH and FT4 levels is needed for this reason and also to avoid the incidence of prolonged phases of supraphysiological thyroid hormone levels [94]-[100].

Recommendation 54: Levothyroxine should be initiated once a newborn has a positive screening, even before the result of a confirmatory test. In cases where screening tests are borderline, a treatment decision can be postponed until the results of the confirmatory tests return.

Recommendation 55: Tailoring the dose based on the severity of initial TSH and T4 deficit may be the most reasonable approach. In mild cases: a dose of 8 to 10 mcg/kg/day is recommended. Higher doses may be required for infants with severe congenital hypothyroidism. (12.5 to 15 mcg/kg/day).

Recommendation 56: A Dosing regimen based on age:

- Full-term newborn: a dose of 10 - 15 mcg/kg/day
- Preterm newborn: a dose of 10 - 15 mcg/kg/day, though in milder cases, often characterized by delayed TSH elevation, a starting dose of 8 to 12 mcg/kg/day
- Age 1 to 3 years - 4 to 6 mcg/kg body weight
- Age 3 to 10 years - 3 to 5 mcg/kg
- Age 10 to 16 years - 2 to 4 mcg/kg

OR

Dosing regimen is based on body surface area calculated at 100 kg/m^2/day

Recommendation 57: The aim of therapy in **infants** is to maintain the serum TSH in the mid-to-upper half of the pediatric reference range and the serum thyrotropin in the mid-to-lower half of the pediatric reference range. The target should be to normalize serum thyroxine approximately 2 - 4 weeks after initiation of therapy. Once the proper dose is identified, surveillance testing with a serum TSH and FT4 should be performed every 1 - 2 months during the first year of life with decreasing frequency as the child ages.

The aim of therapy in **children** is to normalize their biochemical parameters and reverse the signs and symptoms of hypothyroidism.

Pregnancy: In ongoing pregnancies, hypothyroidism has been associated with a high risk of various complications. These complications include placental abruption, preeclampsia, gestational hypertension, preterm labor, increased chance of cesarean section, postpartum hemorrhage, and neuropsychological and cognitive impairment in the newborn child. About 14 studies calculated the population-based pregnancy-specific reference ranges for TSH. Korevaar *et al.* showed

that in nearly 90% of all studies, the upper limit for TSH was above 2.5 mU/L. ATA 2017 guidelines suggested determining pregnancy-specific and lab-specific reference ranges for TSH. For hypothyroid pregnant women, serum TSH levels should be assessed every 3 - 4 weeks during the first half of pregnancy and every 6 - 10 weeks afterward. The LT4 dose should be modified to keep the serum TSH below 2.5 mU/L. TSH and free T4 levels should be measured 3 - 4 weeks after every dosage adjustment [101]-[110].

Preconception counseling is essential in this regard. Studies have reported that nearly 30 percent of women taking LT4 have a TSH level > 4 mU/L when they show up for their first prenatal visit. In such women, serum TSH of (4.5 - 10) compared with <2.5 mU/L is a forecaster of miscarriage (95% CI 1.03 - 3.14). Nearly 50% - 85% of women with preexisting hypothyroidism require high LT4 doses during pregnancy. Another study showed that 17% of women with preconception TSH values < 1.2 mU/L needed a dose increase during the following pregnancy, compared with 50% of women with preconception TSH levels between 1.2 and 2.4 mU/L [111]-[116].

Recommendation 58: Treatment of women with overt hypothyroidism with levothyroxine replacement therapy is recommended. The dosing should be titrated to achieve a target TSH serum level.

Recommendation 59: TSH target in pregnancy is in the lower half of **the trimester-specific reference** range. If not possible, target TSH levels are below 2.5 mU/L.

Recommendation 60: Serial TSH levels should be assessed every 4 - 6 weeks during the first half of pregnancy for dosing adjustment of levothyroxine to maintain TSH levels within the target range. During the second half of pregnancy, TSH should also be reassessed.

Recommendation 61: In women on levothyroxine who are planning pregnancy, TSH level should be evaluated preconception, and doses adjusted to achieve a TSH value between the lower reference limit and 2.5 mU/L.

Recommendation 62: For women already on levothyroxine therapy, increase the total daily dose by approximately 25% - 30%.

Estrogen therapy

Recommendation 63: Reassessment of TSH serum level after 4 - 8 weeks if estrogen therapy is initiated or discontinued, as it may alter the levothyroxine requirement. Interval is 6 to 12 weeks after starting estrogen therapy.

Hospitalized patients:

Recommendation 64: For patients who are on levothyroxine therapy and unable to take enteral levothyroxine, It can be given intravenously until enteral absorption improves. The dose should be approximately 70% - 80% of the patient's oral dose.

Also, it may be given via nasogastric tube using extemporaneous preparation or rectal route using a hospital-prepared levothyroxine suppository.

Poorly compliant patients: The efficacy of a single weekly dose was assessed in a crossover trial that included 12 patients. On administration of a single

weekly dose, the mean TSH concentration was higher than when the usual daily dose (6.6 versus 3.9 mU/L), but the elevated value normalized one day after the next weekly dose. No difference has been observed in symptoms between daily and weekly dosing [117].

Recommendation 65: For patients who do not respond to efforts to improve adherence to daily oral levothyroxine, a total weekly oral administration (7 times the daily dose) may be given.

Levothyroxine allergy: Most patients on LT4 therapy tolerate the medication without unfavorable adverse effects because LT4 is identical to the hormone released in the body. Nevertheless, few patients recognize adverse reactions from the treatment, including headaches, tachycardia, anxiety, and other nonspecific symptoms. A reasonable attempt in such cases would be to lower the LT4 dose and increase it slowly. One report of symptoms recorded symptoms resolution when the concurrent iron deficiency was corrected. Highlighting that the correct acknowledgment of the reason for symptoms is challenging. Allergy to the dye in the tablet may infrequently occur and can be resolved using 50 mg, dye-free tablets. An allergy report presented a rash that appeared in a patient taking an LT4 formulation made in Korea and having tartrazine yellow no. 4 and red no. 3 was bypassed by giving the patient a different LT4 product. If problems continue, refer the patient to an allergist to rule out other causes [118] [119] [120].

Recommendation 66: For patients with apparent allergy to levothyroxine, changing the dose, formulation, and brands, by treating concomitant iron-deficiency anemia or an allergist consultation could be reasonable approaches.

5.1.10. Combination T4 and T3 Therapy

There is no sufficient rationale to support its benefits over T4 monotherapy, uncertain safety profile, and multiple daily dosing [121].

Recommendation 67: We do not suggest the routine use of combined T4 and T3 therapy to treat primary hypothyroidism.

5.2. Managing Subclinical Hypothyroidism (Definition, Management, Follow-Up)

5.2.1. Candidates for Treatment

Data discussing the pros and cons of LT4 treatment in patients with serum TSH levels (4.5 - 10 mU/L) is scarce. Treatment in patients with lower serum TSH concentrations may improve nonspecific symptoms of hypothyroidism, such as lethargy and constipation, and may diminish the goiter size if present. This recommendation was made by the NICE panel based on their experience. Some experts recommend that the existence of cardiovascular-disease risk factors may endorse treatment [122] [123].

Recommendation 68: When discussing whether or not to start treatment for subclinical hypothyroidism, consider features that might suggest underlying thyroid disease, such as symptoms of hypothyroidism, previous radioactive iodine treatment or thyroid surgery, or raised levels of thyroid autoantibodies.

Adults: Even though nearly all experts suggest the treatment of patients with serum TSH levels > 10 mU/L, the routine treatment of asymptomatic patients with TSH levels of (4.5 - 10 mU/L) stays debatable. This recommendation is in harmony with the suggestions of a clinical consensus group including representatives from the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) also with the European Thyroid Association guidelines [7] [99] [100] [124] [125] [126] [127].

It was raised that dependence on serum TSH levels to make decisions about treatment is common in clinical practice, which may be problematic. Other factors, including patients' symptoms, are to affect their demand for therapy. The committee saw that a trial period of 6 months of therapy would be suitable for symptomatic patients with TSH lesser than ten mlU/L. Based on their previous experience, the committee decided that therapy was less likely to have a benefit but that the risk-benefit ratio was most beneficial for adults under the age of 65. The committee stated that adults over 65 were less likely to experience symptoms improvement and the harm potential from suppressing TSH is high. The committee approved that the trial of LT4 therapy should be stopped if symptoms continue with TSH levels within the reference range, as this may be due to reasons other than hypothyroidism[76] [128].

Recommendation 69: Consider levothyroxine for adults with subclinical hypothyroidism who have a TSH of 10 mU/litre or higher on 2 separate occasions 3 months apart.

Recommendation 70: Consider a 6-month trial of levothyroxine for adults under 65 with a TSH above the reference range but lower than 10 mU/litre on 2 separate occasions 3 months apart, and symptoms of hypothyroidism.

Recommendation 71: If symptoms do not improve after starting levothyroxine, re-measure TSH. If the level remains raised, adjust the dose. If symptoms persist when serum TSH is within the reference range, consider stopping levothyroxine and follow the recommendations on monitoring untreated subclinical hypothyroidism and monitoring after stopping treatment.

Recommendation 72: Follow-up and monitoring as patients with primary hypothyroidism

Pregnant: Evaluation of antibody status is essential because women with subclinical hypothyroidism and positive TPO-Ab manage to have the greatest risk of adverse pregnancy consequences, and adverse outcomes happen at a lesser TSH than in women without TPO-Ab. The ATA systematic review (ATA guidelines on thyroid disease during pregnancy) stated that the risk of pregnancy-specific complications was clear in TPO-positive women with TSH > 2.5 mU/L but was not steadily clear in TPO-negative women until TSH values surpassed 5 - 10 mU/L. In some studies, treatment of TPO-Ab-positive pregnant women with normal thyroid function with LT4 improved abortion rates. Nevertheless, in a meta-analysis that included 3 studies of LT4 treatment initiation in the first trimester of pregnancy, there was no effect of LT4 on miscarriage. However, a significant reduction in the preterm labor rate was observed. A prospective study

included 115 euthyroid patients showed that TPO-Ab patients. Half were randomly allocated to LT4 (median dose 50 mcg daily), and half did not receive treatment; a comparison was made with 869 euthyroid, TPO-Ab-negative patients. Mean baseline TSH was higher in the TPO-Ab positive women and significantly higher during the pregnancy in the untreated TPO-Ab positive women than in the LT4-treated, TPO-Ab positive women [108] [129]-[134].

Recommendation 73: Pregnant women with TSH concentrations > 2.5 mU/L should be evaluated for TPO-Ab status.

Recommendation 74: Initiate low dose of levothyroxine treatment in a pregnant patient with subclinical hypothyroidism. A dose of only 50 mcg/day is typically required for effective treatment of subclinical hypothyroid women.

Children: Most pediatric patients with subclinical hypothyroidism will not progress to overt hypothyroidism, and no significant risk appears with no treatment. In a gigantic, retrospective study that included 121,052 pediatric patients aged from 6 months to 16 years of age, 73.6% of participants with a TSH (5.5 - 10 mU/L). Their TSH returned to normal on five years of follow-up. In participants with a TSH > 10 mU/L, 40% normalized their TSH levels, 33.1% of their TSH values declined, and no more than 25% maintained or increased their TSH level. Besides the lack of Rationale reflecting a high risk of progression, no short-term or long-term complications accompanying untreated pediatric subclinical hypothyroidism, no adverse effect on growth, and no rise in cardiovascular risk or cognitive problems [135]-[142].

Recommendation 75: Treatment is generally not recommended when the TSH is 5 - 10 mU/L.

And

Levothyroxine replacement may be reasonable for patients with TSH > 10 mU/L with signs and symptoms consistent with primary thyroid disease and/or risk factors associated with progression,

Or

- For patients above 2 years

1) TSH level of ≥20 mU/L.

2) TSH level between 10 and 20 mU/L on 2 separate occasions 3 months apart.

3) TSH level between 5 and 10 mU/L on 2 separate occasions 3 months apart, and thyroid dysgenesis, or signs or symptoms of thyroid dysfunction.

- For children aged between 28 days and 2 years who have a TSH level ≥ 10 mU/L. This recommendation is based on NICE guideline [50].

Recommendation 76: Start levothyroxine lower doses (e.g., 25 - 50 mcg) if the patient has subclinical hypothyroidism.

Recommendation 77: Follow-up and monitoring as patients with primary hypothyroidism.

5.2.2. Monitoring for Untreated Patients

Recommendation 78: Follow up **untreated**/stopped adult patients with subclinical hypothyroidism by measuring TSH and free T4 once a year if they have features

suggesting underlying thyroid disease, such as previous thyroid surgery or raised levels of thyroid autoantibodies, or once every 2 to 3 years if they have no features suggesting underlying thyroid disease.

Recommendation 79: Follow up untreated children over 2 years old and adolescents' patients with subclinical hypothyroidism < 10 mU/L by measuring TSH and free T4 every 3 to 6 months if they have features suggesting underlying thyroid disease, such as thyroid dysgenesis (an underdeveloped thyroid gland) or raised levels of thyroid autoantibodies, or every 6 to 12 months if they have no features suggesting underlying thyroid disease.

Recommendation 80: Follow up untreated children less than 2 years old and adolescents' patients with subclinical hypothyroidism < 10 mU/L, by measuring TSH and free T4 every 1 to 3 months.

5.2.3. Monitoring after Stopping Treatment

Recommendation 81: Follow up with adults' patients with subclinical hypothyroidism who stopped treatment, by measuring TSH and free T4 once a year if they have features suggesting underlying thyroid disease, such as previous thyroid surgery or raised levels of thyroid autoantibodies, or once every 2 to 3 years if they have no features suggesting underlying thyroid disease.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Florid Autonomic Features Associated with Medullary Lacunar Stroke

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Abstract

Introduction: Autonomic nuclei affection results in variations in hemodynamics, temperature, sweating and ECG. Medullary strokes are challenging in their presentation, bizarre clinical signs, work and neurological outcome. The commonest cause is infarction of the posterior inferior cerebellar artery (PICA). Anatomical areas affected include the inferior cerebellar peduncle, dorsolateral medulla, nuclei of the Trigeminal, vestibular nuclei, Ninth and Vagus nerves. The descending sympathetic tracts and spin thalamic tracts. Serious cardiopulmonary events can complicate 11% of cases. Case Presentation: A middle-aged female developed sub-acute dizziness associated with vomiting and right head pains. She was unable to walk but remained cognitively clear. Her gastrointestinal symptoms were disabling and this was the main factor for presenting to the emergency room. The risk factors included hypertension and diabetes mellitus. Imaging studies were essential for posterior circulation stroke diagnosis and follow-up. She manifested remarkable autonomic features regarding the skin and hemodynamics. Nevertheless, the hospital course was controllable. **Discussion:** This case report was consistent with relevant literature in the contra lateral vaso motor changes and drop in body temperature during the acute phase. Moreover, our patient developed clinical and radiological extension through double antiplatelets. Superiority of the magnetic resonance imaging (MRI) scans in this patient enabled better diagnostic accuracy in a brainstem stroke. **Conclusion:** The autonomic features, in this case, represent major symptomatology and clinical signs. The variation in the hemodynamics and persistence of symptoms is thought provoking. This increases the awareness of emergency doctors for acute stroke presenting with autonomic features will enable early detection and helps outcome.

Keywords

Autonomic, Medullary Infarction, Wallenberg's Syndrome, Brainstem Stroke

1. Introduction

Stroke is the major neurological disorder across the world affecting communities and health systems. It has significant impact on patient's physical ability and quality of life. Autonomic disturbance was described with central and peripheral insults, mainly stroke and Guillain Barre' syndrome. Cerebrovascular disease of the brainstem can cause central temperature, hyperhidrosis, cardiopulmonary and ECG changes, Cheyne-stokes breathing or sleep apnoea, Spinal lesions were associated with episodic hypertension [1] [2]. Infarction of the posterior inferior cerebellar artery (PICA) is the most famous form of medullary infarction known also as Wallenberg's syndrome/Lateral medullary syndrome. This affects middle-aged population and lateral medullary syndrome has a more favorable outcome than medial medullary as demonstrated in a large series which enrolled 387 patients [3]. In this cohort, uncontrolled diabetes and atherosclerosis were the more common independent risk factors for medial medullary syndrome than lateral medullary syndrome. The vertebral artery may be responsible in other cases. Pathological damage involves the inferior cerebellar peduncle, dorsolateral medulla, descending spinal tract, neucli of the trigeminal and Vagus nerves, descending sympathetic tracts, ventrolateral tract (spinothalamic), vestibular nuclei and ninth cranial nerve [4]. The symptoms include vertigo, ipsilateral facial pain, ipsilateral Horner's syndrome, bulbar weakness, ipsilateral ataxia, contralateral thermoanesthesia and reduced sensations [5]. Though the clinical phenotype of PICA is uniform among patients but individual patients' manifests individual variations [6]. This was confirmed further by matching the lesion topography and neurophysiological testing of brainstem reflexes. Although the afferent branch of the reflexes was always affected, patients showed variations in responses [7]. The risk of fatal cardiopulmonary autonomic dysfunction was found in a previous report to be 11% in the acute phase of lateral medullary infarction while the relapse of stroke during the follow-up period was uncommon [8] [9]. Headache may be the most common symptom of PICA ranging from 54% - 76% [10]. Previous studies targeting patients with lateral medulla infarctions documented the frequent long-term reduction of body temperature and vasomotor changes on the contralateral side consistently in the acute phase, at one month and at 6 months [11] [12].

Thermography was found to be a useful tool to differentiate between pontine infarction and Wallenberg's syndrome using the body service temperature [13]. Commonly, sympathetic over activity is more reported in medullary infarction than the parasympathetic features [14]. The first is caused by direct damage of the sympathetic tracts within the infarcted core while the parasympathetic signs result from either irritation of the superior Salivatory nucleus or disparity between the neuronal discharges between autonomic inputs. The sympathetic nervous system may not affect the cerebral blood flow velocity or mean arterial pressure in patients with infarction of the lateral medulla [15]. Moreover, the Hemorrhage within the lateral medulla may rarely contribute to myocardial in-

jury [16] [17]. Other mechanisms of autonomic dysfunction in patients with cerebrovascular disease demonstrated a relation to atherosclerosis and inflammation reflecting a possible multifactorial background [18].

The outcome of pure lateral medullary infarction was compared to other syndromes of lateral medullary infarction plus other areas infarcted in a large number of patients (248). It was found that the short-term outcome of the lateral medullary infarction pure was better than lateral medullary plus (extra lateral medullary lesions) patients. Interestingly, the long-term outcome was better in patients with lateral medullary infarction plus. The localization of the lesion in both groups affected the final outcome [19]. Patients with pure lateral medullary infarction tend to have more residual symptoms of dizziness, dysphagia and sensory changes than others [19]. Poor prognostic features in medullary stroke were investigated in a multi-center study which included 179 patients. They found that poor long-term results and all cause mortality were not uncommon in medullary infarction. Age, dysphagia and recurrent strokes were the main predictors for that [20].

The objective of this case report is to reflect the possibility of a serious localization stroke presenting with uncommon symptoms. The overlook of the diagnosis may lead to delay in management and investigation with parallel disability. It is important to increase the awareness of emergency physicians that the brainstem stroke may present with acute dysautonomia which may be life-threatening. The modern medical technologies must be utilized to monitor the clinical scenario changes and upgrade patient's care if needed.

2. Case Presentation

This 45-year-old female from an Asian descent, presented with 3 days history of a sub-acute dizziness. The condition was associated with right face pain and right occipital headache that was moderate to severe sometimes. Her dizziness was not associated with tinnitus or hearing impairment. However, she had right ear deafness due to childhood infection. Moreover, she has hypertension and diabetes for few years for which she was taking relevant medications. The patient symptoms worsened over 3 days and she developed repeated vomiting. Moreover, she described occasional periods of remarkable sweating of her trunk on the right side. On further questioning, there were no neck pains, visual symptoms, facial numbness, mouth deviation, voice changes or swallowing issues. She reported no limb symptoms but being too dizzy to walk. The clinical examination showed an average weight and height female with blood pressure of 182/92 mmHg and RBS of 184 mg/dL.

She was conscious, and oriented with normal speech and memory. There was right partial ptosis with small size reactive pupil on the right side. There was asymmetrical oedema and redness of the right cheek. The patient had evidence of left facial nerve weakness (2/5) which was of lower motor neuron (LMN) but had no ipsilateral ear signs. There were normal bulbar nerves as well as fundi.

She had no postural tremors, but her right hand was clumsy and there was a pronator drift on the right side. Her hand tapping and dysdiadochokinesia testing were normal while the finger nose test showed mild distal tremors and subtle ataxia.

She had pale cold left hand and forearm as well as the left leg and foot while sensations were normal (**Figure 1** and **Figure 2**). During the admission period, she was always covering her right side with a blanket to reduce the sense of coldness.

The peripheral pulses were well appreciated as well as sensations for the pin prick (PP), vibration sense (VS), and touch. Tendon reflexes were depressed even with re-enforcement while planters were bilaterally withdrawal. There was no urinary incontinence.

Observation of the blood pressure showed erratic fluctuations in the systolic BP mainly.

The patient had normal routine blood tests but HB A1c and random blood sugar (RBS) were high as well as the fasting lipid profile. The initial CT Brain was reported as normal (**Figure 3** and **Figure 4**) while the MRI diffusion showed a lateral right lacunar medullary infarction (**Figure 5** and **Figure 6**).

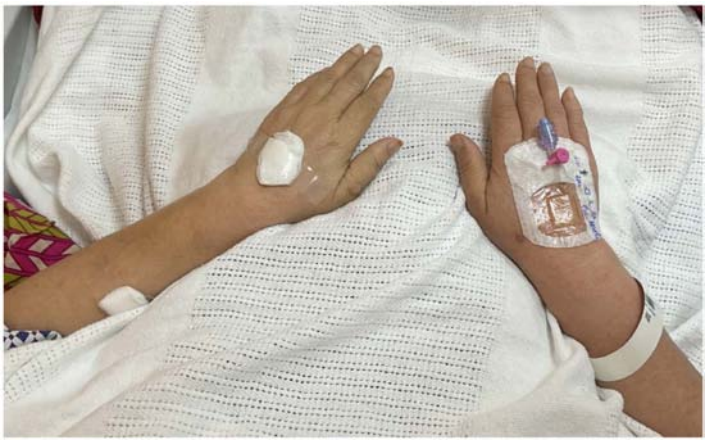


Figure 1. Showing right upper limb pallor in pronation position.

Figure 2. Showing right upper limb and hand pallor in supination position.

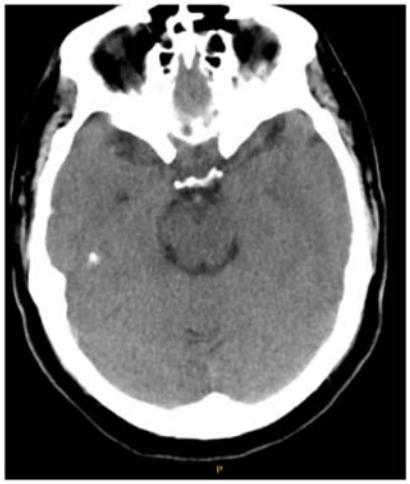


Figure 3. A non-contrast brain CT showing no acute vascular insult.

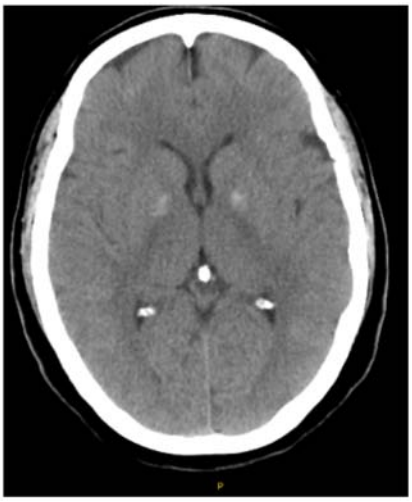


Figure 4. Accidental basal ganglia calcifications.

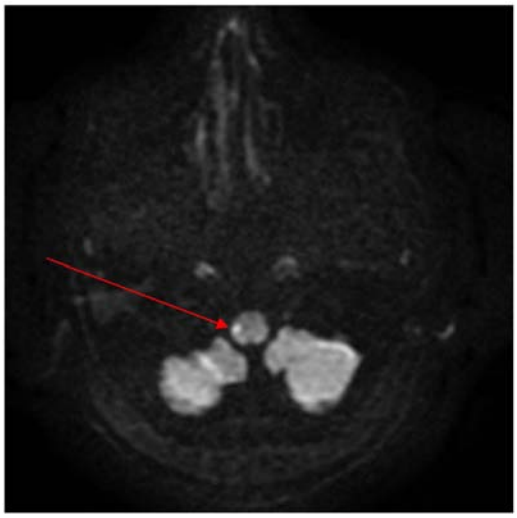


Figure 5. Showing diffusion MRI sequence with lateral medullary acute ischemia. The hyper intense signal in the lateral medulla is indicated by the red arrow.

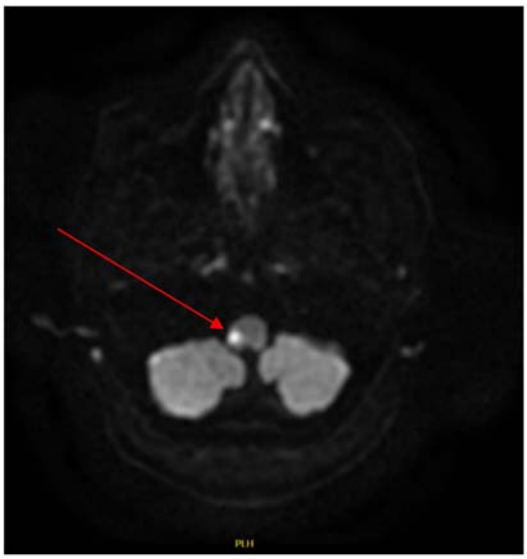


Figure 6. Extension of the infarction is shown. Increase in the size of the hyper intense signal in the lateral medulla is indicated by the red arrow.

The patient was started on aspirin, clopidogrel, statins, Betahistine tabs plus enoxaparin DVT prophylaxis and balance exercises. Her Echo was normal and Covid-19 PCR test was negative. Two days down the course of admission, the patient developed worsening dizziness, repeated vomiting and pain on swallowing. The re-examination showed a dizzier patient with right palatal weakness but no aspiration.

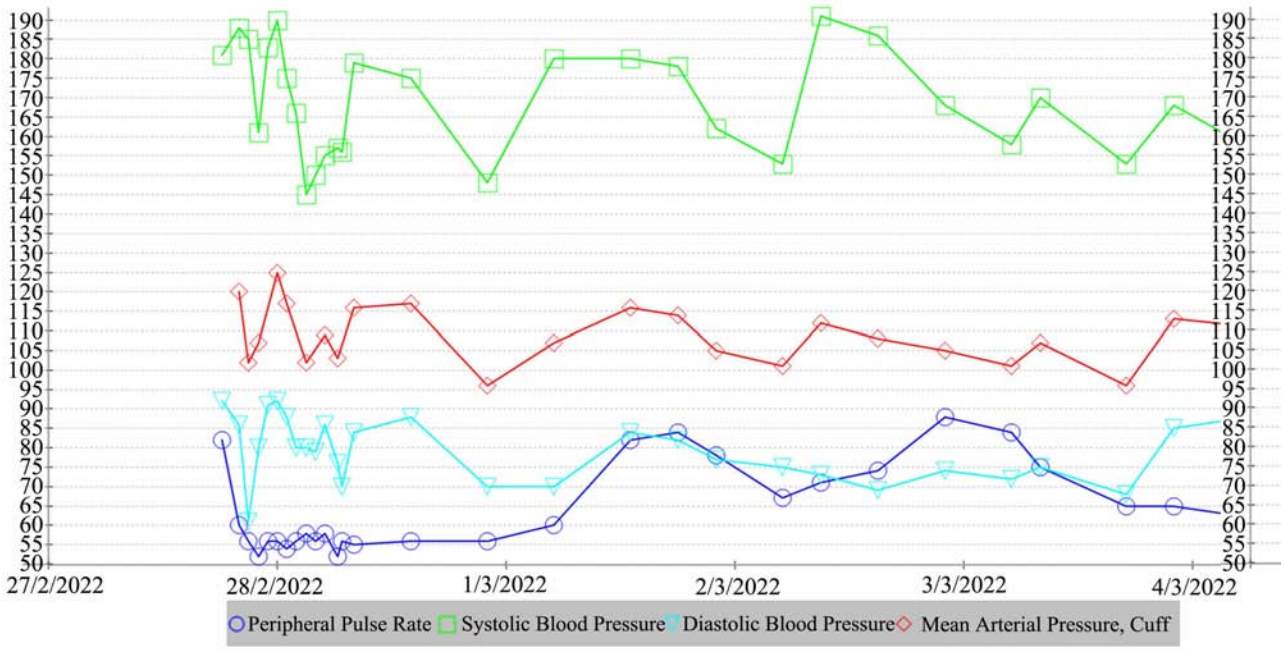
The fluctuations in the heart rate, blood pressure was still persistent, as shown in **Graph 1** below.

The graph represents the blood pressure and heart rate of the patient during her hospital stay. It can be observed that the fluctuations in the blood pressure (systolic, diastolic, and mean) and heart rate were synchronized and changed throughout the day. Where, whenever there was a spike in the blood pressures, the heart rate would also rise, but in variable ranges. Such fluctuations, with the systolic blood pressure ranging from 190 mmHg to 145 mmHg, the diastolic blood pressure scaling between 93 mmHg and 60 mmHg, and the heart rate between 85 bpm and 53 bpm in a small time period can be attributed to central dysautonomia secondary to the stroke.

An urgent repeat of the brain MRI showed expansion of the pre-existing lacunar stroke and no new infarctions or hemorrhages (**Figure 3** and **Figure 4**).

Symptomatic treatment with metoclopramide, Pantoprazole, increase in the Betahistine dose and a nocturnal dose of Dimenhydrinate was used. The patient was re-assured and continued on combination antiplatelets plus hydration. A brain Computerized Angiography (CTA) was normal. The patient had normal autonomic testing on electrophysiology.

The patient was referred to the physical therapy department as early as possible. She received physiotherapy, swallowing assessment, balance exercises and trial of standing. However, this was not successful due to remarkable dizziness.



Graph 1. Showing the Systolic BP (mmHg), Diastolic BP (mmHg), Mean Arterial Pressure (mmHg) and the Heart Rate (beats per minute—bpm) during the patient's hospital stay.

Frequent sessions and encouragement were provided to facilitate the functional outcome.

A neuropsychological assessment was done on day five of admission. Her grooming was adequate and she was cooperative with the examination. The patient reported that her mood was "Good" while her affect was mildly constricted. The speech had little delay with normal tone and average volume. Our patient was coherent and goal directed with intact higher functions. Her proverb interpretations were clear as well as judgment, reliability, and insight. The patient expressed mild guilt feeling related to neglecting her physical health that lead to an extent to her current state. She denied any other mood symptoms. This patient showed good motivational effort talking about rehabilitation and recovery. Hamilton depression rating scale was done and she scored (3/17) which is within the normal range. There was no evidence of formal thought disorder or abnormal thought content. She did not have any past psychiatric history or family history. Reassurance was done along with motivation to start the rehabilitation journey with the team.

The clinical condition of the patient improved slowly over 3 days and on discharge, her dizziness reduced to a limit and she remained with florid symptomatic right side autonomic skin features and right Horner's syndrome.

The patient was reviewed in the neurology outpatient department 5 weeks later. She attended on a wheelchair and reported that her dizziness is still troubling. The modified Rankin Scale was 4. Moreover, there were left body burning sensations. The residual signs included the facial swelling and redness though less, Horner's syndrome, pallor of the left upper and lower limbs. The patient was

adherent to medications and her vital signs were within normal levels. The patient continued on the medical recommendation and exercises. A round six months down the course of stroke, she was able to walk without support though not back to baseline, do her daily home activities, the right hemi-sensory symptoms are almost gone and burning sensation is now negligible. The modified Rankin score became almost 1.

3. Discussion

The manifestation of vascular risk factor as a stroke is a common encounter in neurology practice. However, the uncommon localization reflects a challenging diagnostic, intervention and management puzzle [21]. This case of lateral medullary infarction is similar to other reported cases in the main symptomatology of dizziness, Horner's syndrome, vomiting and subtle pyramidal symptoms. It is also consistent in localization to the lateral medulla. However, the patient in this case report manifested more uncommon features like the minimal ataxia, preserved speech initially, absent ipsilateral ear symptoms, florid vasomotor changes on the contralateral side and the fluctuations of the BP over the first week of admission. The chronic right ear deafness since childhood is the likely cause in the absence of right ear symptoms of tinnitus and deafness.

Moreover, she developed extension of the infarction at day three despite the use of combination of anti-platelets and good hydration. Though the management followed the current recommendations of treating minor strokes in the acute stroke best practice [22] but the extension may have reflected the status of her collateral circulation and activity of the risk factors. Another point to mention here are the rapid fluctuations of the systolic blood pressure secondary to the stroke related central dysautonomia. Literature had included development of atrial arrhythmias like supra ventricular tachycardia following a left insular stroke [23] as well as ventricular arrhythmias [24].

This case report conforms to literature in the persistence of dizziness and disturbing sensory symptoms almost 3 months following this pure lateral medullary infarction [19]. On the other hand, it differs fortunately in the non-development of cardio respiratory arrest and need for ICU care [9].

The risk of relapse of ischemic stroke is related to multiple factors and time linked. Swallowing dysfunction escalates the disability scale and compromises cognitive function and this is associated with extension of the damaged brain tissues [25]. This was investigated in a study performed in a stroke unit investigating the association. This reported case had good prognostic signs including age and absence of dysphagia as proved in a multi-center study [20]. Hence, it was important after the development of swallowing symptoms to perform radiological re-evaluation in this case which was consistent with the new symptomatology. Our patient is similar to other cases in the presence of penetrating artery disease (PAD) as the commonest mechanism of meduulary infarction as revealed by her Brain CTA [26].

The recognition of the vasomotor changes secondary to the autonomic tracts

ischemia in this syndrome is essential for addressing the diagnostic problem, localization and patient's concerns. Affection of the autonomic fibers with unbalanced neuronal discharges from the parasympathetic fibers will be the likely explanation despite a normal peripheral autonomic testing. It is also an important clinical sign to recognize and differentiate pontine versus medullary ischemic lesions. The early recognition and management will add to the better outcome.

The daily bedside evaluation of acute stroke phase is of paramount importance in detecting serious complications like extension of the infarct. This is guided by the basic medical tools of history and examination. The details of which revealed the deterioration in dizziness, worsening vomiting, headache and new onset dysarthria and discomfort on swallowing. The superiority of the MRI scan here carries a high diagnostic value and helps in determining of further endovascular interventions in cases out of the thrombolysis window [27]. From the patient's prospective, this will determine more on prognosis and outcome.

The learned lesson from this case is that whenever dizziness is associated with new onset focal neurological signs, a central cause should be suspected. The normal CT image should not distract emergency doctors from serious vascular conditions. Moreover, the florid autonomic features should not be missed even if the patient is not recognizing it. This is meant to raise doctor's awareness of critical neurological examination in relevant cases. It is essential to use modern imaging techniques to re-evaluate a patient who deteriorated while still on secondary prophylaxis of stroke.

4. Conclusion

Attention to atypical stroke presentation is essential as it remains the leading cause of adult disability. Judicious and timely use of modern imaging techniques will have a good impact on management and outcome. Unexplained gastrointestinal symptoms may be related to a central cause. While new onset dizziness deserves critical imaging in patients with vascular risk factors. The presence of new onset autonomic symptoms and signs can guide the clinical diagnosis of brainstem stroke. Close monitoring of such patients will guard against serious cardiac and respiratory complications.

Acknowledgements

We acknowledge the consent given by the patient to publish this case report.

Ethical Approval and Consent Participate

Ethical approval was obtained from the research ethical committee of the ministry of health and prevention (EHS) UAE for the publication of the case report and upper limb photos. The patient willingly provided her written consent for publication and photos.

Availability of Supporting Data

Data are available in the electronic database of Al Qassimi Hospital Sharjah UAE

and kept confidential as per the regulations of the Ministry of Health and Prevention (MoHAP).

Authors' Contributions

Dr. Muaz Elsayed who is a senior consultant neurologist and an adjunct clinical professor, came with the report idea, did the literature search and wrote the Abstract, literature, discussion and references. He shared writing the case presentation. Dr. Akram Harazeenwho is a general practioner, wrote the vital signs section in the case presentation and designed the graph. Dr. Asma Bin SHAMS who is a psychiatry resident, did the psychological assessment, and wrote it. Dr. Pournamy Sharathchandran who is a senior consultant neurologist, shared the clinical management of the patients and edited the text. Dr. Firas Alrawi who is a neurophysiology consultant, did the Autonomic testing and wrote the section related in the case presentation. Dr. Tayseer Zain who is the head department of neurology, and Dr. Samia Noor who is a neurology specialist, shared the management and follow-up of the patient.

Conflicts of Interest

No conflicts of interest.

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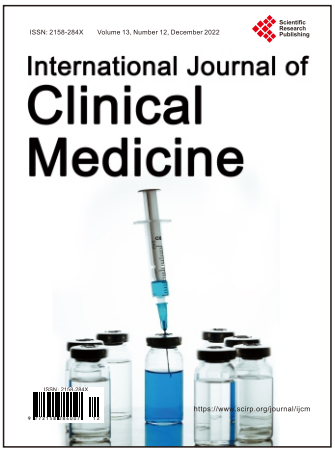

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