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Hyperhomocysteinemia: Risk Factors and Faster Onset of Degenerative Complications of Type 2 Diabetes in Brazzaville

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Abstract

Background: Type 2 diabetes (T2D) remains a major global public health problem. This complex metabolic disorder can lead to various complications, including cardiovascular diseases (leading cause of death) in T2D. Among the biochemical markers associated with increased risk for cardiovascular disease, homocysteine is currently one of the predictive markers under evaluation. We investigate the link between hyperhomocysteinemia and diabetes complications in DT2 population in Brazzaville. **Methodology**: We conducted a cross-sectional analytical study, from October to December 2022. One hundred and fifty participants were included, 100 patients T2D (34 with complications, 33 with comorbidities, 33 without), and 50 patients controls. Sociodemographic and clinical characteristics were collected. Homocysteine (Hcy) serum levels were measured using Sandwich ELISA method. **Results**: Study population was composed of 50% males and 50% females with sex ratio of 1; mean age was 52.2 ± 10.8 years (30 - 83). The prevalence of hyperhomocysteinemia (HHcy) was 36% (20% moderate Hcy, 15% intermediate and 1% severe). Mean Hcy con-

centration was 31.9 µmol/l (18 - 103). Age, gender and physical inactivity were strongly correlated to Hcy (OR of 3.5; 9.4 and 3 respectively). Multivariate analysis showed that HHcy was a risk accelerator for degenerative complications (stroke: OR = 6.2; ischemic heart disease: 4.9; neuropathy: 9.2; retinopathy: 4.5 and peripheral arterial disease: 4.9). **Conclusion:** These findings suggest that hyperhomocysteinemia can be considered as a predictive marker to be taken into account in targeting cardiovascular risk in Congolese subjects with T2D.

Keywords

Hyperhomocysteinemia, Patients with T2D, Risk Factor, Acceleration Factor, Degenerative Complications, Congo

1. Introduction

Type 2 diabetes (T2D) remains a major global public health problem. This complex metabolic disorder can lead to various complications. These complications are major concerns and account for increased morbidity, disability, and mortality. The high mortality from cardiovascular disease requires close monitoring to detect and address traditional risk factors such as obesity, hypertension, dyslipidemia and smoking [1]. In addition, among biochemical markers associated with an increased risk for cardiovascular disease, homocysteine (Hcy) is currently one of the predictive markers under evaluation. Studies showed that other risk factors such as decreased folates and cobalamins levels, less frequently considered may play a synergistic role in accelerating diabetes complications [2].

In the last decade, hyperhomocysteinemia (HHcy) has been recognized as a predictor of risk of death or coronary events and its levels have been linked to the existence and extent of metabolic syndrome and the development of atherosclerosis [2] [3] [4]. However, the relationship between hyperhomocysteinemia, risk factors for T2Dand degenerative complications has been source of controversies [5] [6] [7].

Most of studies conducted in the sub-Saharan Africa region, supported the hypothesis of the involvement of hyperhomocysteinemia in cardiovascular and thromboembolic disorders in patients with T2D and in the general population [8].

We conducted the present study in order to investigate the contribution of hyperhomocysteinemia among cardiovascular risk factors and complications in Congolese population of patients with T2D in Brazzaville.

2. Material and Methods

This cross-sectional analytical study was conducted between October and December 2022. Anthropometric parameters (weight, height, BMI) and sociodemographic data (age, gender, smoking, sedentary lifestyle and family history of diabetes mellitus, hypertension, obesity and hyperlipidemia) of patients with diabetes were collected using a pre-established survey form. All T2DM patients with diabetic complications (macro and microvascular); with or without comor-

bidities; and those without any complications, were included alongside a control nondiabetic control group. Patients with factors known to modulate serum Hcy level (renal insufficiency, liver disease, hypothyroidism, cancer) were excluded. A total of 150 subjects were included divided as follows: 100 patients with T2D (34 with diabetic complications, 33 with comorbidities, and 33 without complications nor comorbidities), and 50 subjects representing the control group.

After a fasting period of 12 hours, 5 ml of blood were collected in an EDTA K3 tube from patients recruited respectively at the Medical Center DIABC@RE and at the Metabolic and Endocrine Diseases Department of the University Hospital of Brazzaville. After processing and conditioning, samples were sent to the Biomedical Training, Research and Analysis Laboratory of the Faculty of Health Sciences for determination of serum Hcylevels ((PHOMO automated system, using a sandwich ELISA micro-fluidic immuno-chromatographic technique). Data were collected in Excel 2013 and analyzed using SPSS® software (version 20.0). Continuous variables were expressed as mean ± standard deviation and discontinuous variables as frequency and percentages. Multivariate analysis was used to study the association between Hcy and other variables. A statistical test was considered significant for a p-value < 0.05.

3. Results

The characteristics of the study participants by age and gender are summarised in Figure 1. The mean age was 52.2 ± 10.8 years (range 30 to 83 years). The most represented age-range was 50 - 60 years, followed by 39 - 49 years. There were as many men as women with a male to female (M/F) ratio of 1.0 (Figure 2). Regarding socio-demographic characteristics, 70% of the study population was sedentary ($p < 0.0291$); 59% had normal BMI; 31% had BMI below normal and 10% above normal. Among associated prevalent comorbidities (Table 1), hypertension was the most common (69.7%), followed by chronic rheumatic fever (9.1%), and dyslipidemia (6.1%). In T2D patients with micro and macrovascular complications, diabetic neuropathy was the most frequently observed complication (29.43%), followed by diabetic retinopathy (23.5%); stroke (17.6%);

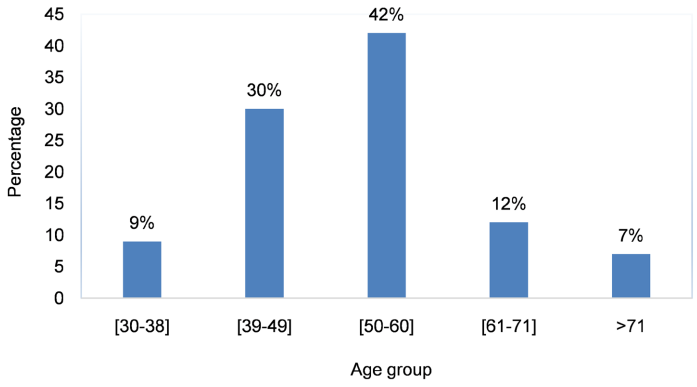

Figure 1. Age distribution of the study population.

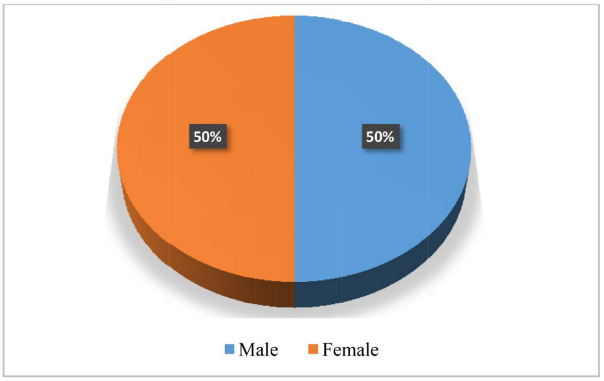

Figure 2. Gender distribution of the study population.

Table 1. Mean homocysteinemia in the 3 subgroups of the study population.

Subgroups	homocysteinemia (µmol/l)		
	Moderate (15 - 30); (N = 20)	Intermediate (31 - 100); (N = 15)	Severe (>100); (N = 1)
T2DM with Comorbidities (N = 7)	20.37 ± 3.7 (n = 6)	33.1 (n = 1)	-
T2DM with Complications (N = 21)	24.27 ± 2.6 (n = 6)	43.57 ± 12.4 (n = 14)	102.6 (n = 1)
T2DM without comorbidities or complications (N = 8)	23.38 ± 4.1 (n = 8)	-	-

Normal value: [Hcy] = 5 - 15 µmol/l.

ischemic heart disease and/or peripheral arterial disease (14.7%); diabetic nephropathy (5.9%); diabetic nephropathy without renal insufficiency or moderate renal disease (2.9%).

The prevalence of HHcy was 36% in the study population. The mean concentration of Hcywas 31.9 µmol/l (range18 to 103 µmol/l). Table 1 shows the frequency distribution of HHcyamong subgroups of the study population: 21.2% in patients with comorbidities; 61.7% in those with complications, and 24.2% in those without neither comorbidities nor complications. In Table 2 are presented the main potential risk factors/markersof HHcy in relation to socio-demographic and anthropometric aspects. Age (OR = 3.5), gender (OR = 9.4) and physical inactivity (OR = 3) were found to be strongly associated with HHcy. Table 3 lists comorbidities as potential risk factors/markers for HHcy. Only hypertension emerged as potential risk factor/marker (OR = 2.5). On the other hand, Table 4 shows the risk incurred by patients with HHcy. In these patients, HHcy increased the odds of degenerative complications such as stroke (OR = 6.2), diabetic neuropathy (OR = 11.9) and retinopathy (OR = 5.8). As regards ischemic heart disease and peripheral arterial disease, the odds was lower (OR = 3.2 respectively).

Table 2. Hyperhomocysteinemia and associated sociodemographic and anthropometric aspects, in T2DM.

		Hyperhomocysteinemia		OR	95% CI	p-value
		Yes	No			
Gender	**Male**	25	25	3.5	1.5 - 8.4	0.003
	Female	11	39			
Age (year)	**>60**	16	5	9.4	3.1 - 29.1	0.000
	<60	20	59			
Sedentary lifestyle	**Yes**	30	40	3	1.1 - 8.3	0.0291
	No	6	24			
BMI (kg/m²)	**<25**	7	24	0.4	0.1 - 1.1	0.0609
	[25 - 30]	25	34			
	>30	4	6	1.2	0.3 - 4.5	0.781

Table 3. Hyperhomocysteinemia and associated comorbidities, Riskfactorsin T2DM.

		Hyperhomocysteinemia		OR	IC à 95%	p-value
		Yes	No			
Comorbidities						
Hypertension	Yes	23	26	2.5	1.1 - 6	0.016
	No	13	38			
Dyslipidaemia	Yes	2	2	1.8	0.2 - 13.5	0.5516
	No	34	62			
CARs	Yes	3	7	0.7	0.1 - 3.5	0.7421
	No	33	57			
CKD	Yes	0	0	-	-	-
	No	36	64			
Obesity	Yes	0	0	-	-	-
	No	36	64			

Table 4. Hyperhomocysteinemia as an accelerating risk factor for complications in T2D.

Complications		Hyperhomocysteinemia		OR	IC à 95%	p-value
		Yes	No			
Stroke	Yes	6	2	6.2	1.1 - 32.5	0.016
	No	30	62			
Neuropathy	Yes	10	2	11.9	2.4 - 58.2	0.0002
	No	26	62			
Retinopathy	Yes	8	3	5.8	1.4 - 23.6	0.0071
	No	28	61			

Continued

AOMI	Yes	5	3	3.2	0.7 - 14.6	0.1035
	No	31	61			
Ischaemic heart disease	Yes	5	3	3.2	0.7 - 14.6	0.1035
	No	31	61			
Nephropathy without IR	Yes	1	2	0.9	0.1 - 10.1	0.9221
	No	35	62			
Coronary artery disease	Yes	0	0	-	-	-
	No	36	64			
Nephropathy with IR	Yes	0	0	-	-	-
	No	36	64			

4. Discussion

This cross-sectional study evaluated the relationship between HHcy as cardiovascular risk factor/marker and frequency of degenerative complications of T2D. The prevalence of HHcy was 36% in the study population, being moderate in 55.5%, intermediate in 41.6% and severe in 2.77%. These results are in line with those of several African studies that observed a high prevalence of moderate HHcy in T2D. We did not carry out a meta-analysis of these, yet our results show a lower frequency than those reported in Ivory Coast and Mali, at 73.68% and 61% respectively [9] [10]. We found higher prevalence than those reported from Senegal (29.4%) [11] by Cisse *et al*.; Togo (44.8%) [12] by Grunitzky *et al*.; and Tunisia by Ferjani *et al*. (23.3%) [13], El Oudi *et al*. (35.6%) [14] and Chadli *et al*. (47.5%) [15].

A link between HHcy and T2Dcomplications has been confirmed in the present study. Someauthors did not make the same finding. Fekih *et al*. [16] showed that Hcy levels were within normal range in patients with diabetes compared to the significantly higher levels in controls. Mazza *et al*. [7] reported low level of Hcyin-patients with T2D, suggesting that these reduced levels could be explained by the detrimental effects of chronic hyperglycemia on renal function or by the acceleration of hepatic transsulfuration pathway due to decreased insulin sensivitiy and/or secretion. Our findings tend to support the hypothesis that poor glycemic control and prevalent degenerative complications of T2D may contribute to HHcy driving a heightened risk of incident degenerative complications in T2D [17] [18] [19].

It was reported that HHcy is a stronger risk factor/marker of vascular complications among patients with T2D than in non-diabetic subjects [20] [21] [22]. Some authors pointed out that HHcy is not the sole consequence of dysglycemia, but is also linked to other risk factors associated with T2D complications/comorbidities, although this was not a generalized opinion [23].

The concept of a higher prevalence of HHcy in patients with hypertension in

certain populations is emerging [24], even though the explanation for this association remains hypothetical. We found a strong relationship between hypertension, stroke and HHcy among patients with T2D aged 40 - 60 years. Several studies have found a higher mean Hcy level in relation to age. Some have established the kinetic increase of Hcy concentration throughout the age range 20 - 70 years [9] [13] [25]. The consistency of the link between an increase of Hcy and risk factors could be ascribed to physiological loss of renal function over time [26], gastric atrophy, and/or inadequate intake of vitamins and folates, observed in elderly subjects [27].

Gender is another factor that may influence Hcy level. Ours results showed that mean Hcy levels were 25% higher in men and 11% in women. This difference is much less than those of similar studies carried out in Africa reporting HHcy rates of 52.2% and 52.63% respectively in Beninese and Ivorian men and women [5] [28]. Some data in the literature confirm this increase of this biomarker in men compared with women [11] [29].

A sedentary lifestyle was 70% prevalent in the present study. Only 42.8% ofcases were statistically significantly associated with Hhcy. These results are in line with data from the literature, which support the hypothesis that physical inactivity contributes to elevate Hcy [30]. It should be noted, however, that we found no link between obesity and Hcy.

In the same time, a link has been established between moderate HHcy and increased cardiovascular risk, notably coronary artery disease and stroke, although biases have led to this risk being overestimated [31]. Our results concur with those of many authors such as Mabchour *et al.* [32] in Benin and of YayaGoita in Mali [33], who found a relationship between HHcy and hypertension. However, some authors have found no major relationship between HHcy and incidence of hypertension [34]. A link between HHcy and risk of early-onset stroke has been reported by other authors [10] [31] [35].

The multivariate analyses related to the group with T2D degenerative complications found significant difference according to Hcy levels. Thus, HHcy was strongly associated with diabetic neuropathy (OR = 11.9) and retinopathy (OR = 5.8). This is in line with data from the literature that report higher levels of Hcy in T2D patients WITH retinal and renal damage [21] and ischemic heart disease [36]. Poor glycemic control and prevalent micro and macrovascular complications may also have modulated Hcy levels in this study.

An increased mortality rate from cardiovascular disease in patients with T2D and HHcy levels was reported by many authors such as Buysschaert *et al.* [20]. Similar results have been reported in experimental studies as well. Several mechanisms were proposed according to which HHcy could promote vascular wall damage through direct cytotoxicity on the endothelium, smooth muscle cell proliferation, lipid peroxidation of LDLs, decreased nitric oxide (NO) production, and pro-coagulant effects involving platelet activity and various coagulation factors [18] [37].

5. Conclusion

Homocysteine should be considered as a cardiovascular risk factor/marker in relation to T2D in a Congolese population. Based on our findings, we suggest that this biomarker could be considered as predictive marker of complications to be taken into account in management of modifiable cardiovascular risk in Congolese subjects with T2D. A multicenter prospective and randomized study could help address other aspects of HHcy, including the role of genetic polymorphisms.

Knowledge on the Subject

Homocysteine is currently a cardiovascular risk factor/marker in patients with type 2 diabetes.

Scientific Contribution of This Study

This study contributes to the identification of a new risk factor/marker and early-onset complications among Congolese patients with type 2 diabetes in Brazzaville.

Conflicts of Interest

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

Authors' Contributions

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Data processing: Wilson Fabrice Ondongo.

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