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The Role of Hyperinsulenemia as a Risk Factor for Pancreatic Cancer*

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ABSTRACT

Background: Pancreatic cancer is associated with a very severe prognosis and identification of risk factors is essential. Diabetes and obesity are both established risk factors, and they both cause hyperinsulenemia. With this review we wished to appraise the evidence of a role of high insulin levels in causing pancreatic cancer. **Methods:** We searched PubMed, Embase, Cochrane Library and Medline, and all evidence on potential pathophysiology of hyperinsulenemia and pancreatic cancer was included. Meta- and pooled-analysis on epidemiological evidence are reported, as well as individual studies were as appropriate for specific topics (role of therapies, central adiposity and role of physical exercise). **Conclusion:** Hyperinsulenemia, and possibly hyperestrogenism secondary to a metabolic syndrome, are important elements in the pathogenesis of pancreatic cancer. Modification of certain life-style factors (exercise and weight loss) appears to modify the risk of pancreatic malignancy.

Keywords: Pancreatic Cancer; Obesity; Diabetes; Risk Factors; Hyperinsulenemia

1. Introduction

Worldwide, pancreatic cancer is the 13th most common cancer but the 8th most common cause of death with little improvement in survival over the last few decades [1]. Surgical resection remains the only potentially curative treatment, but it is feasible in approximately 15% - 20% of patients, as the majority present with metastatic diseases [2]. Five-year survival in the operated patients is around 10% - 15%, and the overall median survival for those with metastatic disease at presentation averages at 6 months [3,4]. To date screening remains unfeasible and it is therefore crucial to identify and correct the risk factors associated with the development of pancreatic cancer.

Cigarette smoking is a well-established risk factor [5], but only a quarter of cases of pancreatic cancer are being attributed to it [6]. It is also recognized that diabetes mellitus can be both a cause and a consequence of pancreatic malignancy [7] (**Figure 1**) [8-10]. More recently it has been suggested that there is sufficient evidence of an increased risk of pancreatic cancer in obese patients [11], with increased body adiposity being an independent risk factor for the malignancy (**Figure 2**).

These are all potentially reversible risk factors, and therefore great emphasis should be placed on implementing prevention.

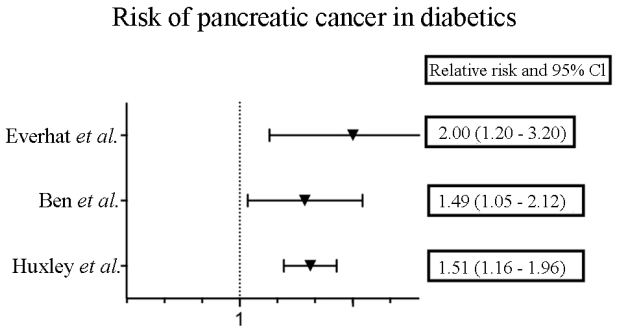

Figure 1. Relative risk and 95% confidence interval (CI) of pancreatic cancer for diabetic patients with disease duration between 5 to 10 years [8-10].

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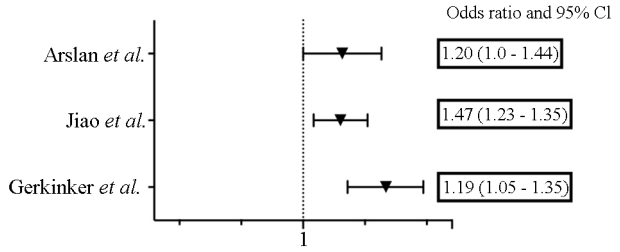

Figure 2. Odds Ratio and 95% confidence interval for class 1 obese patients (BMI > 30 and <35) versus individual of normal weight (BMI < 25) [12-14].

Obesity and diabetes have in common increased levels of circulating insulin. In fact the combination of insulin-resistance, reduced glucose tolerance and hyperinsulinemia is typical of adult diabetes, but it is also present independently in obese individuals in what is known as "metabolic syndrome" [12].

In this review we wished to summarize the evidence linking hyperinsulenemia and pancreatic cancer, which we think is highly relevant given the epidemic of diabetes and obesity across the world.

2. Methods

2.1. Obesity and Hypeinsulenemia

The common ground between obesity and diabetesappears to be a higher insulin level. Looking at obesity in fact it seems quite clear that increased adiposity increases insulinemia through what is known as "metabolic syndrome" [13-15].

The adipose tissue has effectively endocrine functions, regulating free fatty acids metabolism and releasing cytokines and hormones, which have effects on distant targets [16]. There is also evidence to suggest that obesity can cause cancer in multiple sites and that a central role appears to lie with hyperinsulinaemia [11,17].

In the presence of excess adiposity, an imbalance is generated as a result of an increase in circulating fatty acids, resistin and Tumor Necrosis Factor-α (TNF-α) by adipose tissue, and reduced release of adiponectin [18,19]. This increases the sensitivity of peripheral cells to insulin (reduced insulin tolerance) and hyperinsulenemia. Higher levels of adiponectin have been associated with a reduced risk of pancreatic cancer in smokers [20].

2.2. The Role of Insulin in Pancreatic Cancer

Insulin is per se an anabolic hormone, promoting cell growth directly by binding on target cells [21]. The exocrine pancreatic tissue is particularly exposed to it through a portal system from the insulin producing islet cells [22]. This exposure is enhanced by the effect of insulin in increasing localized pancreatic blood flow [23]. A tumorigenic effect on pancreatic tissue has been proved both *in vitro* [22,24,25] and in animal models [26-31].

Insulin can also act indirectly through an increased production of Insulin-like Growth Factor 1 (IGF1). In fact, both insulin and IGF1 can promote cell growth and inhibit apoptosis [32,33]. Activation of IGF1 receptors has been shown to increase pancreatic cells proliferation [34].

A study examined the expression of 2 neoplastic markers, cytokeratin and Ki67, in pancreatic ductal epithelia from 45 human autopsy and 9 surgical pathology specimens. Obese non-diabetic individuals ductal cells appeared to replicate 10 times more than in lean non-diabetic, whereas, in lean diabetics, the replication rate was 4 times higher than lean non-diabetic [35]. So it appears that markers of pancreatic ductal replication were increased synergistically in obese diabetic subjects.

Ding *et al.* found that physiologic concentrations of insulin increased pancreatic cancer cell proliferation and glucose utilization by activating mitogen-activated protein kinase, phophotidyl inositol-3 kinase, and glucose transporter1 expression [36].

Three prospective studies have directly investigated abnormal glucose metabolism and the risk of pancreatic cancer. Cumulatively, they reported an increased risk with increasing levels of glucose intolerance, regardless of clinical diabetic status [37-39].

2.3. Diabetes, Its Treatment and Pancreatic Cancer

If an increased level of endogenous insulin is associated with a higher risk of pancreatic malignancy, then insulin treatment could also potentially affect this risk.

This was addressed for the first time in 2003 with a case-control study, which assessed if diabetics treated with insulin therapy were more likely to develop pancreatic cancer than those not treated with insulin [40]. It was found that although diabetes was associated with a 2.86-fold increase in the risk for pancreatic cancer, the risk increased to 6.49-fold for those treated with insulin compared to 2.12-fold for those treated with oral hypoglycemic agents. Furthermore, although the duration of insulin treatment had no effect on the high relative risk (RR), longer duration of oral hypoglycemic therapy was associated with a lower RR for the development of pancreatic cancer. This trend was also observed in a multi-centric case-control study, involving 823 patients with pancreatic cancer and 1679 controls [41]. Diabetics with a diagnosis of between 2 - 9 years had an odds ratio (OR) of 1.58, but those who had been treated with insulin had an OR of 3.54, whereas those who had been treated only with oral medication had an OR of 1.78 (**Figure 3**).

An overview of the mechanisms responsible for hyperinsulenemia is summarized in **Figure 4**.

The key factors therefore appears to be insulin-activated enhancement of cell proliferation, and the central role is probably played by insulin/insulin-like growth factor-1 (IGF-1) receptor in the regulation of neoplastic degeneration [42,43].

Further indirect evidence comes form the protective effect of Metformin.

Metformin activates the liver kinaseB1 (LKB1)-adenosine monophosphate protein-activated kinase (AMPK) pathway, which inhibits the signaling mechanisms that regulate cellular proliferation [44,45]. LKB1 is a known tumor suppressor, which activates AMPK, a potent inhibitor of mammalian target of rapamycin complex 1, and disrupts cross talk between insulin/IGF-1 receptors and G protein-coupled receptors, which regulateprotein synthesis and replication [46-48]. These pathways are criticalregulators of cell replication and have been found to be inhibitedby metformin in pancreatic cancer [26].

2.4. Hyperinsulenemia and Estrogen Levels

Another indirect effect of hyperinsulemia is the increased synthesis and bioavailability of both male and female sex hormones [49]. Adipose tissue is the main source of oestrogens in both male and post-menopausal females. In particular, synthesis of oestone and oestradiolare increased and liver production of a sex-hormone binding globulin is reduced. The latter results in an increased bioavailability of both oestrogens and testosterone.

In severely obese men the increase of testosterone drives a negative feedback, inducing a reduced produc tion of gonadotrophin and an increased conversion of testosterone into oestogens. The net effect is an increase

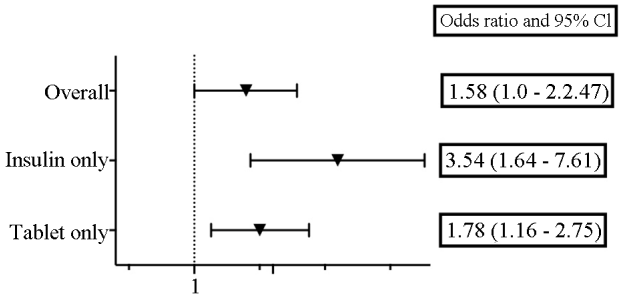

Figure 3. Odds ratio and 95% confidence interval (CI) for patients with diabetes mellitus (overall), for those who had been treated with insulin only, and for diabetic patients treated with tablets only.

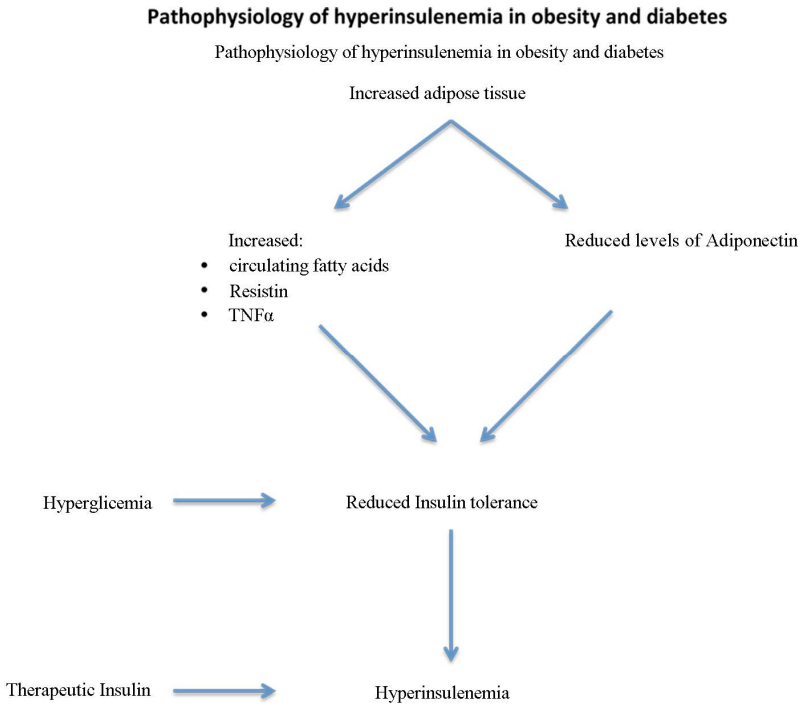

Figure 4. Pathophysiology of hyperinsulenemia in obesity and diabetes.

in oestrogens in obese male individuals [49]. A role of hyper-oestrogenism has been suggested in the pathogenesis of cancer [50] and might justify the increase risk of pancreatic malignancy according to parity, age of menarche and possibly oral contraception in obese women compared to normal weight women [51].

2.5. Central Adiposity and Insulin Resistance

Central adiposity is more associated with insulin resistance [52]. Most of the studies that have looked at central adiposity (waist circumference, waist to hip ratio and central torso weight gain) to evaluate risk of pancreatic cancer, had positive findings [53-58]. In a North American cohort, a central weight gain was found to confer significant risk in the development of pancreatic cancer, in comparison to peripheral weight gain [53]. In the AARP study waist circumference was positively associated with pancreatic cancer in women, independently from body mass index (BMI). This, however, was not observed in men. Furthermore, no association was found in relation to waist to hip ratio [57].

2.6. Physical Activity and Pancreatic Cancer

Physical activity has been shown to improve glucose tolerance and insulin resistance, independently from its effects on weight [59,60]. A large study that addressed this topic in relation to pancreatic cancer, involving 2 cohorts of patients, found that physical activity reduced the risk of pancreatic cancer, particularly in overweight patients [61]. However only high levels of physical activity have been found to reduce risk [62,63].

In a meta-analysis, both waist circumference and waist to hip ratio were moderately associated with pancreatic cancer risk [64]. Two pooled analyses demonstrated a positive association with waist to hip ratio only [65,66], with a higher risk for women specifically in one study [66].

Two studies involving patients who underwent bariatric surgery are also consistent with the finding that effective treatment of obesity and concomitant diabetes mellitus reduces cancer risk [67,68].

3. Conclusion

Chronic hyperinsulinemia secondary to diabetes or obesity increases the risk of the developing pancreatic cancer. Therapeutic insulin, and treatment with drugs that stimulate insulin secretion, seem to increase the risk of carcinoma by enhanced activation IGF activated signaling pathways. Therapies that reduce insulin levels, such as exercise, weight loss and drugs seem to reduce the risk of pancreatic malignancy. Metformin has a protective effect, by reducing insulin levels and improving glucose metabolism, also due to its specific antineoplastic effects.

High calories intake and poor diabetic control should therefore be tackled at institutional level, in an attempt to reduce the incidence of pancreatic cancer particularly as they can act synergistically.

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