**Metabolic Syndrome, Insulin Resistance, Circadian Disruption, Antioxidants and Pancreatic Carcinoma: an Overview**

Aldo Giudice¹, Anna Crispo¹, Massimiliano Galdiero², Giovanni D’Arena³, Mario Felice Tecce⁴, Maria Grimaldi¹, Alfonso Amore⁵, Emanuela Esposito⁵, Maurizio Montella¹

**INTRODUCTION**

Pancreatic cancer is a devastating disease characterized by an increased incidence in western industrialized countries, an extremely poor median survival of 4-6 months after diagnosis [1] and limited therapeutic options [2]. The incidence and number of deaths caused by pancreatic tumours have been gradually rising, although incidence and mortality of other common cancers have been declining [3]. The inability to detect pancreatic carcinoma at an early stage, its aggressiveness, and the lack of effective systemic therapy are responsible for the rapid death of pancreatic carcinoma patients [4]. Clearly, novel approaches to human pancreatic carcinoma therapy are needed. Recently, it was shown that PPARγ ligands such as antidiabetic thiazolidinediones (e.g. pioglitazone and rosiglitazone) inhibit the growth of pancreatic carcinoma both *in vitro* and *in vivo* [4]. Suppression of tumor angiogenesis may be one of the mechanisms by which PPARγ activation inhibits the growth of pancreatic carcinoma [4]. In addition, antidiabetic thiazolidinediones may also induce ductal differentiation but not apoptosis in pancreatic cancer cells [5]. Risk factors for this malignant disease include cigarette smoking, family history of chronic pancreatitis, advancing age, male sex, diabetes mellitus, obesity, non-0 blood group, a high-fat diet, alcohol consumption and possibly *Helicobacter pylori* and hepatitis B virus infections. Metabolic diseases have become the leading cause of death in many countries. Our paper serves as a focused and updated discussion about the development of novel preventive strategies for this deadly disease.

**ABSTRACT**

The incidence and number of deaths caused by pancreatic tumours have been gradually rising, while the incidence and mortality of other common cancers have been declining. Risk factors for this malignant disease include cigarette smoking, family history of chronic pancreatitis, advancing age, male sex, diabetes mellitus, obesity, non-0 blood group, a high-fat diet, alcohol consumption and possibly *Helicobacter pylori* and hepatitis B virus infections. Metabolic diseases have become the leading cause of death in many countries. Our paper serves as a focused and updated discussion about the development of novel preventive strategies for this deadly disease.

**Key words:** metabolic syndrome – insulin resistance – circadian disruption – antioxidants – pancreatic cancer.

**Abbreviations.** ARE: antioxidant response element; COX-2: cyclooxygenase-2; IGFs: insulin-like growth factors; IGF1R: IGF-1 receptor; MetS: metabolic syndrome; NAFLD: non-alcoholic fatty liver disease; NAFPD: non-alcoholic fatty pancreas disease; NASH: non-alcoholic steatohepatitis; NASP: non-alcoholic steatopancreatitis; PPARγ : peroxisome proliferator-activated receptor γ; PPARs: peroxisome proliferator-activated receptors.
hyperglycemia, dyslipidemia, insulin resistance and diabetes [15]. It is estimated that approximately 25% of the world’s population has MetS. In the United States, MetS is more common in men and Hispanics and its incidence increases with age [16]. Importantly, MetS increases the risk of developing cardiovascular disease and type 2 diabetes mellitus [16]. In addition, there is a growing interest in a potential etiological role for MetS in the development of cancer [17]. Various studies have shown that most components of MetS may independently or in combination increase the risk for developing certain types of cancer [18], such as liver, endometrial, renal cell, breast, prostate and colon cancer [19-25].

**METABOLIC SYNDROME**

Evidence that obesity is linked to pancreatic cancer is increasing [26]. As pancreatic steatosis is related to obesity, non-alcoholic fatty pancreas disease (NAFPD) has been hypothesized to be involved in the development of pancreatic cancer [27]. NAFPD has also been suggested to cause pancreatic cancer via non-alcoholic steato-pancreatitis (NASH), a concept analogous to non-alcoholic fatty liver disease (NAFLD), which can cause hepatic cancer via non-alcoholic steatohepatitis (NASH) and hepatic cirrhosis. In summary, it appears that pancreatic inflammation associated with obesity (pancreatic steatosis) and substantial pancreatic fibrosis, making this organ more susceptible to pancreatitis, may increase the risk of pancreatic cancer [28]. Interestingly, positive associations between pancreatic cancer and more elements of the syndrome, including abdominal obesity, hyperinsulinemia and elevated serum glucose level have also been reported [29-31]. Another important Italian record-linkage study including 43 pancreatic cancer cases reported an overall standardized incidence ratio of 1.62 (confidence interval [CI], 1.17-2.18) for subjects with a combined therapy of hypolipemiant, antihypertensive and hypoglycemic drugs [32] also found a relative risk (RR) of pancreatic cancer of 1.80 (95% CI, 0.94-3.45) in 41 overweight female cases with at least three MetS components, but found no relation in men. With reference to the other factors in MetS, i.e. hypercholesterolemia and hypertension, various studies found no significant relations, consistent with the overall epidemiological evidence [33-36]. In addition to increasing the prevalence of chronic diseases, diabetes is another independent risk factor for the development of pancreatic cancer. However, it is debated whether diabetes is a causal risk factor or, on the contrary, pancreatic cancer causes diabetes [37]. Huxley et al [38] found a two-fold increase of pancreatic cancer risk in diabetics in accordance with a meta-analysis published in 2005 giving a relative risk (RR) of 1.82 (95% CI, 1.66-1.89) in patients with type 2 diabetes [39]. Another Italian case-control study, including overall 688 pancreatic cancer cases and 2204 controls, found an odds ratios (OR) of pancreatic cancer of 2.74 (95% CI, 2.04-3.67), with a stronger association for a more recent diagnosis of diabetes; but the association persisted for at least 10 years before pancreatic cancer diagnosis [40]. A meta-analysis including three cohort studies and one case-control study, found a mean RR of 1.55 (95% CI, 1.19-2.01) for subjects with MetS [39].

**DIABETES AND INSULIN RESISTANCE**

It was recently reported by Li D [37] that the mechanism of the association between diabetes and pancreatic cancer is elusive but is known to include metabolic, hormonal and immunological alterations that influence tumor growth. Importantly, insulin resistance and compensatory hyperinsulinemia as well as elevated levels of circulating insulin-like growth factors (IGFs) are perhaps the most hypothesized mechanisms underlying the association between type 2 diabetes mellitus and pancreatic cancer [41]. Experimental evidence suggests that insulin is a growth-promoting hormone with mitogenic effects [42]. Insulin promotes cell proliferation and increases glucose use, both of which being important to tumor development and progression [43, 44]. Furthermore, insulin upregulates the bioavailability of IGFs by reducing the hepatic production of IGF-binding proteins [42, 43]. The mitogenic and antiapoptotic activities of IGF-1 are more potent than those of insulin and may act as growth stimuli in cells expressing insulin and the IGF-1 receptor (IGF1R) [37, 41]. Importantly, IGF-1 and IGF1R are highly expressed in pancreatic cancer cells [45] and IGF-1-mediated signalling transduction increases proliferation, invasion and expression of angiogenesis mediators and decreases apoptosis in pancreatic cancer cells [46-48]. Data from animal studies also indicate that the islet cell turnover, which is associated with insulin resistance, is critical for pancreatic carcinogenesis [37]. For example, in hamsters, stimulation of islet cell proliferation, enhanced pancreatic ductal carcinogenesis [49], and destruction of islet cells by treatment with streptozotocin or alloxan inhibited pancreatic cancer induction [50, 51].

**HYPOADIPONECTINEMIA**

Another possible mechanism includes the effect of adiponectin, a protein secreted by adipocytes. Interestingly, adiponectin levels are lower in diabetics and are negatively related with plasma glucose and insulin concentration, although it is not clear whether this is a cause or a consequence of insulin resistance [52]. Moreover, hypoadiponectinemia may be considered an independent risk factor for hypertension and also has been associated with an atherosclerotic lipid profile, as it is an independent predictor of high-density-lipoproteins [52, 53]. Therefore, low adiponectin levels are a common characteristic of MetS components. Moreover, adiponectin has been shown to inhibit endothelial cell proliferation and migration [54] and has been involved in the etiology of several cancers [55, 56], particularly pancreatic cancer [57].

**CIRCADIAN DISRUPTION**

An important aspect to consider in pancreatic carcinogenesis is the role of the circadian clock. It is thought to be an important regulator of metabolism and disruption of this clock has been implicated in various pathologies, ranging from obesity, diabetes and MetS to cancer such as pancreatic cancer [58, 59]. Interestingly, MetS has been reported to be associated with a
flattening of molecular clock rhythms in peripheral tissues and with nighttime eating. The relationship between metabolism and the clock is not unidirectional and the two processes are intertwined [60]. One common clinical condition suggestive of interactions between circadian rhythms and metabolism in humans is that of shift work. Numerous reports have indicated that shift workers have a higher incidence of diabetes, obesity, and cardiovascular events [61, 62], although the mechanism underlying this association is uncertain. Recently, Scheer et al [63] tested the impact of forced circadian misalignment (a simulation of shift work) on neuroendocrine control of glucose metabolism and energetics. Specifically, in participants subjected to circadian misalignment, the authors observed hypoleptinemia, insulin resistance, inverted cortisol rhythms and increased blood pressure. It is also interesting to note that patients with diabetes exhibit dampened amplitude of rhythms of glucose tolerance and insulin secretion [64]. Thus, the relationship between circadian disruption and metabolic pathologies appears to be bidirectional in humans, suggesting that circadian disruption may lead to a vicious cycle and contribute to the augmentation and progression of metabolic disease. Other studies have also demonstrated that shift workers have a higher incidence of several cancers including pancreatic cancer [58, 65]. Collectively, these findings are consistent with the idea that the disruption of either the circadian clock or metabolism can lead to derangement of the other, thus predisposing to metabolic disorders such as obesity and type 2 diabetes as well as cancer [56, 58, 65].

**ANTIOXIDANTS**

Recent research also suggests that the intake of several dietary antioxidants (e.g., coenzyme Q, vitamin C and E, selenium) and phytochemicals (e.g., ellagic acid, curcumin, lycopene, epigallocatechin gallate, and resveratrol) that are present in fruit, vegetables, herbs and medicinal plants can prevent cardiovascular abnormalities, neurodegeneration and pancreatic carcinogenesis [66-68]. These phytochemicals not only have direct antioxidant properties but also activate cellular stress response pathways through the induction of kinases and transcription factors, leading to the expression of antioxidants and phase II enzymes [69]. For example, activation of the Nrf2 transcription factor/antioxidant response element (ARE) pathway by these phytochemicals plays a role of great importance in the constitutive and inducible expression of cytoprotective enzymes capable of dramatically influencing susceptibility to carcinogenesis and other degenerative pathologies [69-71]. Interestingly, many herbal or dietary plants also contain several bioactive terpenoids, which can prevent cardiovascular abnormalities, neurodegeneration and pancreatic carcinogenesis [66-68]. These phytochemicals not only have direct antioxidant properties but also activate cellular stress response pathways through the induction of kinases and transcription factors, leading to the expression of antioxidants and phase II enzymes [69]. For example, activation of the Nrf2 transcription factor/antioxidant response element (ARE) pathway by these phytochemicals plays a role of great importance in the constitutive and inducible expression of cytoprotective enzymes capable of dramatically influencing susceptibility to carcinogenesis and other degenerative pathologies [69-71]. Interestingly, many herbal or dietary plants also contain several bioactive terpenoids, which can prevent cardiovascular abnormalities, neurodegeneration and pancreatic carcinogenesis [66-68].

Several studies indicate that the presence of MetS or a greater number of MetS components are associated with a significantly higher risk for all-cause cancer mortality, as well as pancreatic cancer mortality. Interestingly, the key component of MetS in pancreatic carcinogenesis appears to be diabetes. Improved understanding of the pathological mechanisms shared by diabetes and pancreatic cancer would be the key to the development of novel preventive and therapeutic strategies for this deadly disease.

**CONCLUSION**

Several studies indicate that the presence of MetS or a greater number of MetS components are associated with a significantly higher risk for all-cause cancer mortality, as well as pancreatic cancer mortality. Interestingly, the key component of MetS in pancreatic carcinogenesis appears to be diabetes. Improved understanding of the pathological mechanisms shared by diabetes and pancreatic cancer would be the key to the development of novel preventive and therapeutic strategies for this deadly disease.

**Conflicts of interest.** No conflict to declare.

**Authors’ contribution.** A.G. contributed to the conception of the study, A.C. and E.E. to data analysis and manuscript drafting, G.A., M.A., M.F., T. to manuscript revision for important intellectual contents, A.C. and E.E. to data analysis and manuscript drafting, M.Ga., and M.F. to manuscript revision for important intellectual contents, M.G. and A.A. to data acquisition and critical revisions for important intellectual contents. M.M. contributed to conception and design of the study, and offered methodological advice.

**REFERENCES**


J Gastrointestin Liver Dis, March 2014 Vol. 23 No 1: 73-77


64. Boden G, Chen X, Polansky M. Disruption of circadian insulin secretion is associated with reduced glucose uptake in first-degree relatives of patients with type 2 diabetes. Diabetes 1999;48:2182-2188.