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Sporadic Pancreatic Cancer: Glucose Homeostasis and Pancreatogenic Type 3 Diabetes

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Abstract

Sporadic pancreatic cancer (SPC) has been frequently associated with impaired glucose homeostasis manifested by prediabetes, Type 2 diabetes or predominantly by T3c diabetes which develops as the first symptom of cancer. Pathogenic mechanisms in the development of T3c diabetes have not been fully elucidated although specific substances originating in the tumor cells are supposed to be the cause of β -cell dysfunction and insulin resistance. New biomarkers evaluated in patients with recent-onset diabetes are necessary for the early diagnosis of this tumor. Actual data characterizing risk factors, early symptoms, pathogenic mechanisms, biomarkers and structured programs in detection of SPC are described. A multidisciplinary team of primary care physicians, gastroenterologists, endoscopists, radiologists and pathologists should improve the prognosis of this malignant disease.

Keywords: sporadic pancreatic cancer, risk factors, early symptoms, T3c diabetes mellitus, β -cell dysfunction, insulin resistance, biomarkers, multidisciplinary team approach

1. Introduction

Pancreatic adenocarcinoma is a highly malignant cancer which occurs in three different forms: (1) sporadic pancreatic cancer (SPC) accounting for 90% of all pancreatic cancers, (2) familial pancreatic cancer accounting for 7%, and (3) pancreatic cancer as a part of genetic cancer syndromes, which account for the remaining 3%. A detailed program of long-term tertiary prevention (surveillance) is available for the two smaller groups. In contrast, there has been, up to now, no preventive program for the much larger SPC group.

The clinical diagnostics of SPC starts now much as it did in the middle of the past century, that is, after the appearance of local and/or systemic symptoms. They include abdominal and back pain, fatigue, loss of body weight, painless jaundice, anemia, peripheral phlebitis, and cachexia. These symptoms are nevertheless also harbingers of advanced disease.

High-resolution imaging methods (HRIMs: CT, MRI, MRCP, EUS) and histomorphology provide information suitable for diagnostics; nevertheless, their impact on patient prognosis is limited as they are typically ordered at an advanced disease stage. Radical surgery may only be suitable for 15–20% of patients. The relapses are frequent as well as early, and chemotherapy is basically palliative. This confluence of factors results in very low 5-year survival rates of only 3–6% of patients [1].

We recently recommended a screening program for early SPC detection based on cooperation of primary care physicians with gastroenterologists and other specialists [2].

2. Sporadic pancreatic cancer development

Pancreatic carcinogenesis begins with the transformation of pancreatic cells and evolution of the precancerous lesions (precursors). At present, six precursors with different morphologies and malignant potential are distinguished [serous microcystic adenoma (SMA); intraductal papillary mucinous neoplasm (IPMN); intraductal tubulopapillary neoplasm (ITPN); mucinous cystic neoplasm (MCN); pancreatic intraepithelial neoplasm (PanIN); and solid pseudo-papillary neoplasm (SPN)] [3, 4]. The development of SPC based on the gradual accumulation of genetic and epigenetic alterations consists of three stages: (1) time prior to the invasive lesion, (2) time to the development of the metastatic subclone, and (3) time period of metastatic dissemination that leads to patient death. The average duration of the first two time periods is estimated to be about 18 years. Early detection must be concentrated during these two periods, when patients are often without any symptoms [5].

3. Sporadic pancreatic cancer and diabetes mellitus

The association between diabetes mellitus and pancreatic cancer has been repeatedly observed, and several case–control and cohort studies have been analyzed in meta-analyses [6]. The relationship between diabetes and SPC is reciprocal. While long-term diabetes is considered an etiologic/risk factor of SPC, new-onset diabetes may be the first manifestation of SPC [7] as recently summarized by D.K. Andersen [8].

3.1. Type 2 diabetes and obesity: important risk factors

Long-term Type 2 diabetes is a risk factor of SPC with a latency of more than 5 years, and an incidence that is approximately doubled [9, 10]. However, Type 2 diabetes develops from prediabetes and is frequently symptom-free for several years without clinical manifestations, which allows it to go undiagnosed. Exposure to the protumorigenic effects of Type 2

diabetes is in reality often longer than would be expected based on the time point at which the diagnosis was established. Hyperglycemia is the main factor inducing a cluster of events like higher oxidative stress, formation of advanced glycation end products, and inflammation. Such changes increase proliferation, invasiveness, and metastatic potential of pancreatic cancer [11]. Stimulation of receptors for advanced glycation end products (RAGE) promotes pancreatic cancer development, whereas their inhibition was reported to have opposite effects [12, 13]. Hyperinsulinemia exists in prediabetes and in the initial phase of Type 2 diabetes as a consequence of obesity and insulin resistance. Higher intrapancreatic insulin concentrations may stimulate proliferation of pancreatic tumor cells by activating insulin-like growth factor receptors (IGF-1R) and the downstream PI3K/Akt/mTOR signaling pathway [14].

Long-term Type 2 diabetes is frequently associated with *obesity*, which by itself is another independent factor increasing the risk of pancreatic cancer development. Fat tissue as an endocrine organ produces and secretes hormones (adipokines) including leptin and adiponectin, which have been linked to cancer development. The key signaling pathway linking obesity and cancer is the PI3K/Akt/mTOR cascade which regulates cell proliferation and survival [15]. Leptin is positively correlated with adipose stores and nutritional status. It induces cancer progression by activating the PI3K, MAPK, and STAT3 signaling pathways [16]. In contrast to leptin, adiponectin is inversely associated with adiposity, hyperinsulinemia, and inflammation. It exhibits anticancer effects by decreasing insulin/insulin-like growth factor (IGF-1) and mTOR signaling via activation of 5'AMP-activated protein kinase (AMPK) and exerting anti-inflammatory actions via the inhibition of the nuclear kappa-light-chain enhancer of activated B-cells (NF- κ B) [17]. Activation of NF- κ B complex by stimulated RAGE is a possible mechanism through which inflammation may stimulate pancreatic cancer development [18]. In addition, obesity is frequently associated with hyperinsulinemia and may therefore through complex mechanism increase the risk of pancreatic cancer.

3.2. New-onset T3c diabetes: an early symptom of sporadic pancreatic cancer

Newly developed impairment of glucose homeostasis represented either by prediabetes (impaired fasting glucose or impaired glucose tolerance) or diabetes develops as the sole early symptom of SPC and is called pancreatogenic diabetes Type 3c (T3cDM), which appears up to 24 months (or even 36 months according to some investigators) before the clinical manifestation of SPC [19–21]. The relative probability of an already existing undiagnosed SPC is the highest in patients who were diagnosed with impairment of glucose homeostasis within the last 12 months (RR 5.4; 95% CI 3.5–8.3) [22]. A causal relationship between SPC and T3c diabetes is supported by the observation that diabetes resolves after surgical removal of the tumor in more than 50% of patients [23]. However, improvement of glucose homeostasis may be linked to the surgical procedure itself since it has also been demonstrated that subtotal pancreateoduodenectomy similarly improved diabetes in patients with or without pancreatic cancer [24].

T3c diabetes, which represents up to 8% of the total number of patients with diabetes mellitus, can occur secondary to other pancreatic disorders like chronic pancreatitis, hemochromatosis, or cystic fibrosis; however, in these cases, clinical manifestation of exocrine insufficiency usually precedes the development of pancreatic endocrine dysfunction [25]. Pancreatic cancers occur in about 9% of patients with T3cDM [26]. Therefore, one case of SPC per roughly 140

patients with new-onset diabetes can be expected. Patients with new-onset diabetes are associated with a 4- to 7-fold increase in risk of pancreatic cancer, such that 1–2% of patients with recent-onset diabetes were suggested to develop pancreatic cancer within 3 years [27].

4. Pathophysiology of T3cDM associated with sporadic pancreatic cancer

The pathophysiological relationship between T3cDM and SPC remains largely unknown. The high proportion of patients who develop T3cDM as the first clinical symptom of SPC (about 74% patients developing diabetes up to 24 months prior to SPC diagnosis) suggests that the tumor is the cause of the diabetes [28]. In addition, the prevalence of diabetes in patients with SPC is much higher (68%) compared to diabetes that develops in association with other cancers (up to 24%) [29].

4.1. β -cell dysfunction and insulin resistance

New-onset diabetes associated with SPC is a paraneoplastic phenomenon that is characterized by impaired insulin secretion and insulin resistance [30]. Impaired glucoregulation develops gradually. Approximately 15–20% SPC patients are normoglycemic with normal β -cell function but increased insulin resistance. Subjects with impaired glucose tolerance have disturbed β -cell function, but the insulin resistance is not significantly different from the preceding group. The changes in β -cells associated with SPC are initially functional as previously supposed in experimental study [31]. In contrast, morphological changes or a decrease of their counts are associated with other diseases of the exocrine pancreas, that is, chronic pancreatitis, cystic fibrosis, tropical pancreatitis, and hemochromatosis [32].

Several findings support the hypothesis that β -cell dysfunction is caused by substances overproduced by the cancer cells [21], which may impair glucose-stimulated insulin release and contribute to glucose dysregulation. Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine which affects both inflammation and glucose homeostasis. Its overproduction by pancreatic cancer cells has been observed, and its effect on the inhibition of glucose-stimulated insulin release from β -cells as well as from isolated islets, through regulation of Ca^{2+} channels, has also been demonstrated [33]. In addition, increased serum levels of MIF have been found in new-onset diabetic patients with pancreatic cancer while no such increase has been seen in patients with pancreatic cancer without diabetes or in non-cancer new-onset Type 2 diabetic patients [33]. Cancer cells have also been shown to upregulate adrenomedullin, a potent inhibitor of insulin secretion (see below) [34, 35].

In addition to β -cell dysfunction, a significant increase in insulin resistance develops in SPC patients with diabetes [36]. Peripheral insulin resistance was confirmed by hyperinsulinemic clamps in patients with pancreatic cancer and was found to be higher in those with diabetes than in nondiabetic subjects [37]. Improved insulin sensitivity was observed after surgical removal of the pancreatic cancer [37]. Insulin resistance was found to be associated with reduced glycogen synthesis in muscles, which was also confirmed *in vitro* [37]. Impaired glycogen synthesis and glycogen storage in muscles were caused by defects at the post-receptor

level [38]. No changes in receptor tyrosine kinase activity, insulin-receptor substrate (IRS-1), or glucose transporter GLUT-4 were found in skeletal muscle biopsies of pancreatic cancer patients as compared to healthy controls [38]. Muscle insulin resistance was also unrelated to weight loss, plasma free fatty acids, or the energy status of cells and medium conditioned by pancreatic cancer cells did not induce insulin resistance in muscle cells in vitro [39]. Hepatic insulin resistance as determined by HOMA-IR indexes was observed in patients with pancreatic cancer [36]. Hepatic insulin resistance seems to be caused by pancreatic polypeptide deficiency and administration of pancreatic polypeptide has the potential to improve insulin sensitivity in the liver [40, 41]. In addition, adrenomedullin and tumor-derived exosomes may significantly contribute to the development of insulin resistance in SPC patients (see below).

4.1.1. Adrenomedullin

Adrenomedullin secreted by pancreatic cancer cells was found to be an important factor influencing β -cell function. It was first identified in 1993 in a pheochromocytoma as a hypotensive peptide [42]. It binds with three types of specific receptors (ADMR), which belong to the 7-transmembrane superfamily of G-protein-coupled receptors. One of them, the calcitonin receptor-like receptor (CRLR), is modulated by the receptor activity modifying protein (RAMP) [43]. Adrenomedullin is released by pancreatic cancer cells in **exosomes**. These membrane-bound vesicles contain proteins, miRNAs, and other molecules and traffic molecular cargo from the cell-of-origin to target sites in the body. After endocytosis or macro-pinocytosis of adrenomedullin-containing exosomes, adrenomedullin binds to its receptors, initiates endoplasmic reticulum (ER) stress and consequently the intracellular increase of reactive oxygen/nitrogen species (ROS/RNS) that can lead to β -cell dysfunction and death [30]. These observations provide new insights into the relationship between pancreatic cancer and new-onset diabetes. The SPC-associated diabetes was therefore proposed to be an example of an “exosomopathy,” a novel exosome-based disease mechanism [44].

Body weight loss is another symptom frequently accompanying new-onset diabetes associated with SPC. It usually starts shortly after the onset of diabetes, precedes the development of other symptoms, and progresses up to the diagnosis of SPC. Weight loss varies extensively among individual patients with an average loss of between 4 and 5 kg. Weight loss may have a similar paraneoplastic origin as T3cDM. The adrenomedullin-containing exosomes secreted from pancreatic cancer cells interact with adipose cells and are internalized by endocytosis. Adrenomedullin via its receptors activates p38 and ERK1/2 MAPKs and promotes lipolysis through phosphorylation of hormone sensitive lipase [45]; thus, the loss of subcutaneous fat observed in SPC may be a paraneoplastic symptom mediated by exosomal adrenomedullin. Exosome induced β -cell dysfunction and lipolysis could be inhibited by adrenomedullin receptor blockade [30, 45], which underscores the role of adrenomedullin in the development of new-onset diabetes and weight loss in SPC. Nevertheless, exosomes are involved in several other aspects of cancer development including angiogenesis, stromal remodeling, chemo-resistance, and genetic intercellular exchange [46]. Cancer-derived exosomes can also enter muscle cells and inhibit insulin and PI3K/Akt signaling, leading to impaired GLUT 4 trafficking [47]. This effect leading to skeletal muscle insulin resistance may be mediated by microRNAs carried by exosomes [47]. This interaction between pancreatic cancer cells and normal cells represents another example of a “metabolic crosstalk” in

malignant tumors [47]. In additional to the peripheral insulin resistance expressed in skeletal muscles, impaired insulin action has been found in the liver where similar pathogenic mechanisms may be present [32].

4.1.2. *Dipeptidyl peptidase 4 and fibroblast activation protein alpha*

The membrane-bound proteases dipeptidyl peptidase 4 (DPP4, EC 3.4.14.5, CD26) and fibroblast activation protein alpha (FAP alpha, EC 3.4.21.B28, seprase) may represent other factors contributing to impaired glucoregulation in SPC [48]. DPP4 is a membrane glycoprotein expressed on the surface of many cell types including endothelial and epithelial cells, fibroblasts, and activated lymphocytes. Its soluble form is also present in the serum and other body fluids. FAP alpha is a close structural homolog of DPP4 with 52% amino acid sequence identity. Under physiological conditions, the expression of FAP alpha is restricted to alpha cells of pancreatic islets and stromal cells in the uterus. During carcinogenesis, FAP alpha is upregulated in the stromal fibroblasts of various malignancies [49]. FAP alpha positive fibroblasts have been found in primary and secondary cancerous lesions, whereas benign epithelial lesions rarely contain FAP alpha positive stromal cells.

DPP4 and FAP alpha are multifunctional proteins that exhibit both enzyme activity dependent and enzyme activity independent biological functions. The catalytic activity of DPP4 and FAP alpha cleaves off the N-terminal dipeptide from peptides and proteins containing proline or alanine in the penultimate position. In addition, FAP alpha also possesses endopeptidase enzymatic activity, with the potential to cleave among others FGF21 [49]. A number of DPP4 and FAP alpha substrates are related to the regulation of glucose metabolism and energy homeostasis (Table 1). The proteolytic cleavage significantly modifies the biological activity of the targets leading to inactivation, modified receptor preference, or increased susceptibility to cleavage by other proteases [50].

Biopeptide	Main physiological functions	References
GIP*	Stimulation of insulin and glucagon secretion	[78]
GLP-1*	Stimulation of glucose-stimulated insulin secretion, inhibition of glucagon secretion	[78]
PYY**, NPY**	Regulation of food intake, adipogenesis, energy homeostasis, glucose-stimulated insulin secretion, lipolysis and blood pressure. Involved in stress reaction and pain perception	[78–81]
Glucagon*	Increase of glycemia and ketogenesis	[79, 82, 83]
FGF21**	Stimulation of glucose uptake in adipocytes, increase of energy expenditure	[84–86]
VIP*, PACAP*	Regulation of insulin and glucagon secretion, regulation of body weight, energy and lipid metabolism. Gastrointestinal motility. Immunomodulation	[87, 88]

GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; PYY – peptide YY; NPY, neuropeptide Y; FGF21, fibroblast growth factor 21; VIP, vasoactive intestinal peptide; PACAP, pituitary adenylate cyclase-activating peptide.

Table 1. Biopeptides involved in glucose and energy homeostasis that are cleaved by DPP4* and/or FAP**.

The role of DPP4 and FAP alpha has been studied in the context of various malignancies, including pancreatic cancer. Expression of both proteases is increased in SPC tissues and SPC patients with recent onset diabetes or prediabetes have increased plasma DPP4 enzymatic activity [51]. Increased expression and activity of these proteases may thus lead to decreased bioavailability of their substrates and thus contribute to impaired glucose homeostasis in SPC.

In summary, pancreatic cancer cells dysregulate the production of various substances with hormonal or enzymatic activities, which lead to impaired functioning of both the endocrine pancreas and other organs. New-onset T3cDM is therefore a consequence of impaired glucose homeostasis caused by the cancer cells.

5. Diagnosis of T3cDM

Early diagnosis of impaired glucose homeostasis is the first important step in the proper diagnosis of T3cDM associated with SPC. At this stage, the patient is usually without any clinical symptoms and a small decrease in body weight is frequently overlooked or considered unrelated. Determination of blood glucose every 2 years in patients over 50 years is highly recommended as a part of regular preventive examinations by general practitioners. A finding of impaired fasting glucose (IFG) or increased random blood glucose should initiate the next level of examination (i.e., oral glucose tolerance test or HbA1c), which can confirm a diagnosis of prediabetes or diabetes.

The main task for physicians is to distinguish T3c diabetes from the more common Type 2 or Type 1 diabetes, since in general practice only the latter two types are usually considered without any suspicion of T3c. Several indicators can be used for a better evaluation. Firstly, changes in body weight differ in subjects with T2DM vs. T3cDM after the appearance of diabetes. A decrease in body weight at the diagnosis of prediabetes or diabetes is significantly more frequent in patients with T3cDM than with T2DM, likely due to the tumor induced loss of subcutaneous fat tissue [45]. In SPC, the decrease in body weight usually precedes other systemic and local symptoms. T2DM frequently begins with increased body weight associated with insulin resistance and hyperinsulinemia and BMI is often higher compared to T3cDM [8]. A family history of diabetes is common in T2DM but not in T3cDM associated with SPC. The absence of markers of autoimmune disease may help exclude Type 1 diabetes. Therefore, an association of newly diagnosed prediabetes or diabetes with progressive weight loss should lead to the suspicion of T3cDM. Basic laboratory and clinical data that differentiates T2DM and T3cDM are presented in **Table 2**.

The plasma pancreatic polypeptide (PP) concentration in the fasting state and after meal-stimulation may also help discriminate between T2DM and T3cDM [8, 52]. The test is based on increased PP secretion after 30 min of nutritional stimulation in healthy controls and T2DM patients (usually by more than 100% of the baseline value); this increase is missing in T3cDM patients. The discriminative value of this test was found to be higher in cancer of the pancreatic head than in the other regions of the gland [53], since PP-cells are predominantly located within the head of the pancreas.

Indicator	Type 2 DM	Type 3c DM
Body weight	Increase	Decrease
Family history of DM	Positive	Frequently negative
Fasting plasma concentration		
Insulin	High or normal	Low or normal
PP	High or normal	Low or normal
GIP	Normal	Low or normal
Poststimulation levels		
Insulin	High or normal	Low
PP	High or normal	Low
GIP	Normal	Low

PP, pancreatic polypeptide; GIP, glucose-dependent insulinotropic peptide.

Table 2. Clinical and laboratory characteristics differentiating new-onset Type 2 from Type 3c diabetes associated with SPC.

6. Diagnosis of sporadic pancreatic cancer

Failure to diagnose SPC at an early stage is the main impediment to improving the prognosis of patients with this malignant disease. Currently, more than 80% of cases are diagnosed in advanced stages (T3 and T4), which generally excludes radical surgery, the only possibly curative treatment. The prerequisite for early diagnosis of SPC is the timely use of high-resolution imaging methods (HRIMs), which will lead to the identification of patients with early stage, effectively curable disease. The specificity and sensitivity of the classical tumor biomarkers currently used in the clinical practice is low. Therefore, novel biomarkers are critically needed to identify patients in whom HRIMs should be used. Recently, we have proposed a structured diagnostic strategy for individuals with newly diagnosed diabetes, who represent a significant risk group for SPC, involving primary care physicians (both general practitioners and diabetologists) [2].

6.1. Biomarkers

T3cDM with weight loss are alarming signs of a paraneoplastic origin and patients presenting with these signs require further examination. Recent reviews have summarized the present knowledge of biomarkers for the diagnosis of SPC [54–56]. A widely used biomarker, **carbohydrate antigen CA 19–9**, is neither sufficiently specific (68–91%) nor sensitive (70–90%) in patients with SPC and, as such, it is not a reliable marker for screening and early detection [57]. While a more sensitive assay for CA 19–9 has been developed, which also demonstrated higher specificity [58], a combination of different markers in multiplex detection appears to be more promising. A biomarker panel consisting of three proteins: (1) plasma tissue factor pathway inhibitor (TFPI), (2) Tenascin-C (TNC-FN III-C), and (3) CA 19–9, was better than CA 19–9 alone in early-stage cohorts (stage I and IIA/IIB), including the ability to discriminate

stage IA/IB/IIA from healthy controls [59]. This panel had the predictive power to detect early-stage pancreatic cancer and may have clinical utility for early detection of surgically resectable pancreatic ductal adenocarcinoma. In another study, a surface enhanced Raman spectroscopy (SERS) based immunoassay of CA 19–9 in combination with matrix metalloproteinase (MMP7) and mucin (MUC4) in serum had significantly enhanced sensitivity and could be a promising tool for liquid biopsy diagnostics [60].

MicroRNAs, small non-coding molecules circulating in blood, have been tested in patients with pancreatic cancer and healthy controls. They play roles in regulation of cell physiology, tumorigenesis, apoptosis, proliferation, invasion, metastasis, and chemoresistance. Many miRNAs found in serum have been suggested as reliable biomarkers of early SPC detection [61]. Combining several miRNAs with CA19–9 in a composite panel could improve diagnosis compared to a single biomarker. This was documented with six miRNAs (including miR-20a, miR-21, miR-25, miR-155, miR-196a, and miR-210), and CA19–9 [62]. The panels had a high specificity for pancreatic cancer compared to other gastrointestinal cancers and they showed better sensitivity and specificity than CA19–9 alone. A panel of miRNAs could be used to differentiate patients with new-onset diabetes with SPC, healthy controls, and new-onset Type 2 diabetes without SPC [63, 64]. MiRNAs were also analyzed using weighted gene co-expression network analysis (WGCNA). This method better discriminates between healthy and cancer patients and demonstrates that miRNAs can serve as prognostic biomarkers [65]. On the other hand, a set of 15 selected miRNAs was able to discriminate SPC patients from controls at the time of diagnosis but could not be used in earlier stages because their alterations only appeared in the later stages of the disease [66].

Another area of investigation provides new data from **metabolomic** studies that are based on metabolic differences between new-onset diabetes with and without pancreatic cancer as well as in comparison with Type 2 diabetes [67]. Sixty-two metabolites, from several hundred, were analyzed using liquid chromatography/mass spectrometry. The results were able to discriminate between the three abovementioned groups, although the procedure is not yet suitable for routine use. In another study, using a metabolomic profile of 206 metabolites, most significant changes were found in oleanolic acid, palmitic acid, taurochenodeoxycholate, and d-sphingosine, discriminating between healthy controls and pancreatic cancer patients [68].

T3cDM caused by pancreatic cancer is characterized by **abnormal concentrations of several hormones** which participate in glucose homeostasis. In cases where basal plasma concentrations of the hormone are within normal limits, the impairment may be disclosed after mixed-nutrient stimulation [52]. The determination of insulin, pancreatic polypeptide (PP), or glucose-dependent insulinotropic peptide (GIP) during the “meal test” may confirm their decreased levels, which would demonstrate their altered dynamics [19].

Exosomes bring new possibilities to the detection of SPC [69]. The proteins, miRNAs, and mRNAs transferred by these vesicles originating in cancer cells can be used as biomarkers. Several body fluids like serum, urine, and saliva were demonstrated to contain pancreatic cancer-derived exosomes [70]. Exosomes may improve early diagnosis of pancreatic cancer in stage I and IIA when the tumor is still localized [71]. Two miRNAs, miR-196a and miR-1246, were found to be highly enriched in pancreatic cancer exosomes and elevated in plasma exosomes of patients with localized pancreatic cancer. Exosomes can be examined

in pancreatic juice when new-onset diabetes is suspected as a paraneoplastic symptom of SPC [72]. Exosomes trafficking within pancreatic juice may facilitate the development of a pre-metastatic niche well before any symptomology that might support an early diagnosis of pancreatic cancer [72].

It appears that an early diagnosis is increasingly dependent on a combination of biomarkers with sufficient sensitivity to disclose localized tumors or, better still, their precursors.

6.2. Imaging methods

Diagnosis based on visualization of the tumor and classification of its stage is necessary for clinical decisions regarding treatment and the use of high-resolution imaging methods (HRIMs) is therefore immediately recommended in patients suspected of having SPC. The results of different methods were compared using a large database [73]. Effective screening procedures for early detection of pancreatic cancer were described by Hanada et al. [74, 75]. A review of the advances in various imaging methods, as well as their proper selection is beyond the scope of this review.

7. Risk groups of diabetic patients suggested for screening of sporadic pancreatic cancer

Early diagnosis and subsequent successful treatment of SPC associated with diabetes depends on proper evaluation of the **risk groups** of patients >50 years of age:

1. Patients with new-onset prediabetes or diabetes:
 - a. With decreasing body weight (>2 kg) and anorexia as the only clinical symptom
 - b. With failure of introductory antidiabetic drug therapy during the first 3 months and stagnation or a decrease in body weight (>2 kg)
 - c. With persistent impairment of glucose homeostasis despite the additional of a second antidiabetic drug during the next 3 months or a decrease in body weight (>2 kg)
2. Patients with long-term diabetes and obesity when there is a failure of antidiabetic drug therapy that developed during the preceding 6 months combined with a decreasing body weight (>2 kg).

In patients from the first group, the new-onset diabetes and the loss of body weight may be **early symptoms** of SPC. In the second group, long-term diabetes and obesity are **risk factors** for SPC [76]. A decline in diabetes control, as measured by glycated hemoglobin HbA1c, may precede clinical detection of pancreatic cancer by several months up to 5 years [77]. The failure of the antidiabetic drug treatment characterized by either poor or worsening diabetes control is a common feature of both T3c and T2 diabetic patients with pancreatic cancer [21].

Sometimes the fluctuations of blood glucose confirm unstable diabetes regardless of intensified insulin treatment. The findings of (1) worsening diabetes control and (2) failure of anti-diabetic drug treatment indicate the need for SPC screening. Patients in both risk groups (i.e., new-onset and long-term diabetes) should be examined according to the structured protocol we described earlier [2].

8. Protocol for early sporadic pancreatic cancer detection

The program of early SPC detection has three steps [2]:

- a. A clinical suspicion of SPC in the risk groups evaluated by general practitioners (GPs) or diabetologists,
- b. A determination of biomarkers (oncomarkers, microRNAs, etc.) and hormones (GIP, PP, GLP-1) after nutritional stimulation as prescribed by a gastroenterologist,
- c. An endoscopic examination of the patient and use of high-resolution imaging methods (HRIMs) as prescribed by an endoscopist/radiologist in collaboration with a pathologist.

A multidisciplinary team approach should improve the prognosis of this malignant disease. The early symptoms (new-onset T3cDM and weight loss), the effect of the initial antidiabetic drug therapy, as well as the failure of antidiabetic therapy in long-term diabetes control, with newly developing weight loss, should be properly evaluated by a GP or a diabetologist.

We suggested an algorithm for the examination of patients with new-onset diabetes (**Figure 1**) [2]. Regular screening of blood glucose in the general population above 50 years of age may disclose abnormalities in glucose homeostasis. Additionally, the evaluation of body weight and any changes during the months prior to the visit is critical. A decrease in body weight > 2 kg in a patient with newly confirmed prediabetes or diabetes should arouse suspicion of its para-neoplastic origin. In this case, a gastroenterologist should be consulted.

A patient with new-onset diabetes should be treated with the first line antidiabetic drug according to the guidelines for Type 2 diabetes. If the diabetes control is not satisfactory during the first 3 months and body weight remains stable or increases, then a second anti-diabetic drug should be added. An inadequate response to intensified treatment or unintentional weight loss should lead to a suspicion of T3cDM. In this situation, the collaboration with a gastroenterologist, preferably in a tertiary center, is necessary. The patient should be tested for PP and GIP secretion after nutritional stimulation. A response by PP and GIP that is diminished or absent confirms the pancreatogenic origin of the diabetes (T3cDM). A gastroenterologist should arrange the next steps involving an endoscopic examination and HRIMs.

A patient with long-term diabetes with failing antidiabetic drug treatment combined with decreasing body weight should be included in the same multistep screening program as described for T3cDM patients.

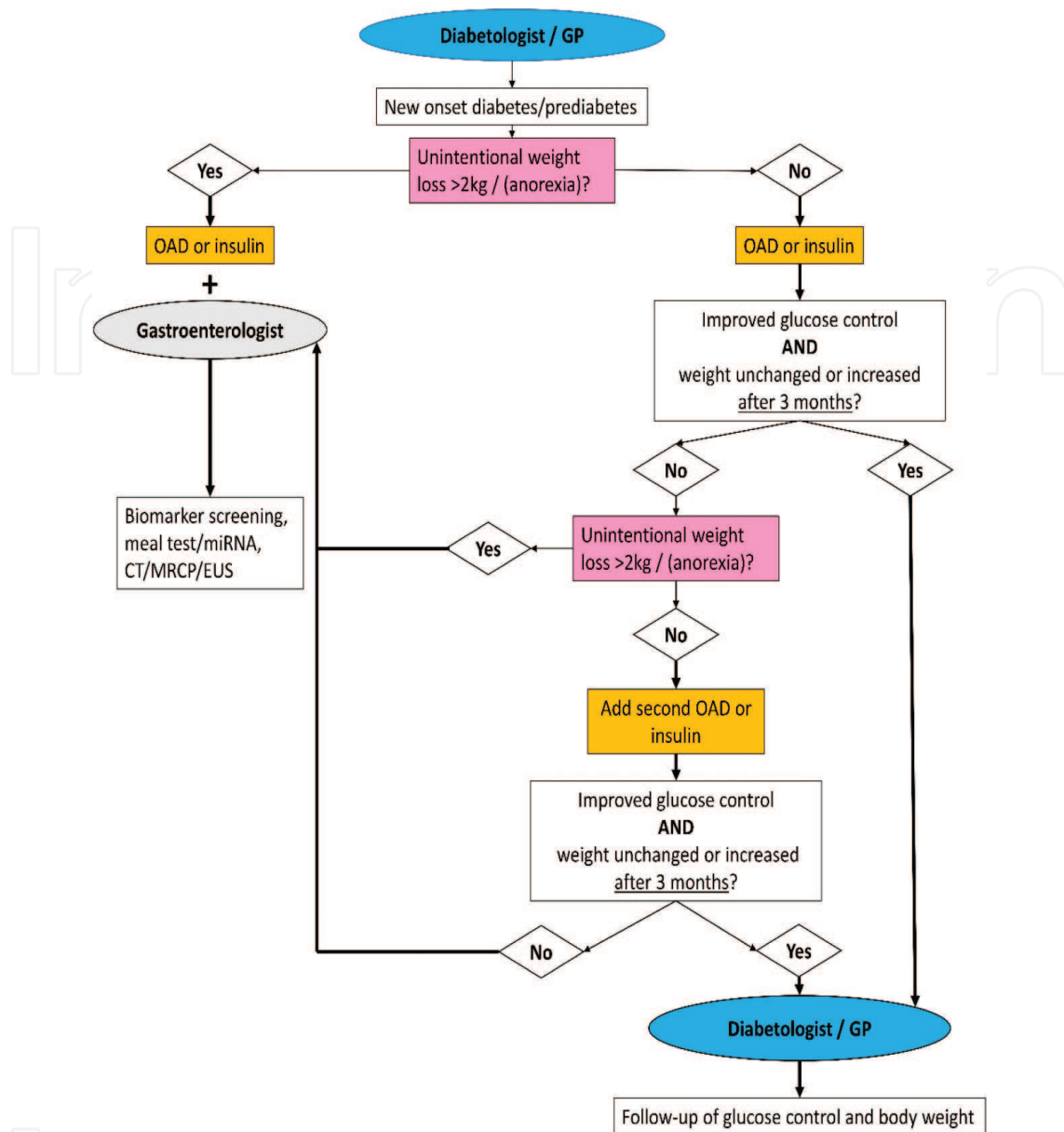


Figure 1. Differential approach to a patient with new onset diabetes/prediabetes. Unintentional weight loss, anorexia or no improvement in glucose control with appropriate treatment should prompt an evaluation by a gastroenterologist. OAD, oral antidiabetics; EUS, endoscopic ultrasonography; GP, general practitioner.

9. Conclusion

The association of SPC with diabetes mellitus offers an opportunity for early detection of this malignant disease. While long-term Type 2 diabetes is an important risk factor of SPC, new-onset T3cDM represents an early symptom as well as a pathogenetic feature of SPC. Thus, proper assessment of new-onset diabetes with a focus on the analysis of early symptoms, that is, failure of antidiabetic drug treatment including unstable diabetes requiring insulin administration, represents a promising step in shifting the diagnosis of SPC to an earlier stage. New biomarkers and high-resolution imaging methods may help discriminate between different pathologies with better accuracy, including identification

of the earlier stages of pancreatic cancer. A multistep and multidisciplinary preventive program based on collaboration between GPs, diabetologists and gastroenterologists offers an opportunity for timely SPC diagnosis. This approach may improve the prognosis for these patients.

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Conflict of interest

The authors have no conflict of interest.

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