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BIOCHEMICAL LABORATORY DATA OF TYPE 2 DIABETIC PATIENTS WITH COMORBID THYROID DYSFUNCTION

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ABSTRACT

Thyroid dysfunction and diabetes mellitus are closely linked. Several studies have documented the increased prevalence of thyroid disorders in patients with diabetes mellitus and vice versa. This review critically discusses the different underlying mechanisms linking type 1 and 2 diabetes and thyroid dysfunction to demonstrate that the association of these two common disorders is unlikely a simple coincidence. We assess the current state of knowledge on the central and peripheral control of thyroid hormone on food intake and glucose and lipid metabolism in target tissues (such as liver, white and brown adipose tissue, pancreatic β cells, and skeletal muscle) to explain the mechanism linking overt and subclinical hypothyroidism to type 2 diabetes and metabolic syndrome. We also elucidate the common susceptibility genes and the pathogenetic mechanisms contributing to the autoimmune mechanism involved in the onset of type 1 diabetes mellitus and autoimmune thyroid disorders. An untreated thyroid dysfunction can impair the metabolic control of diabetic patients, and this association can have important repercussions on the outcome of both of these disorders. Therefore, we offer recommendations for the diagnosis, management, and screening of thyroid disorders in patients with diabetes mellitus, including the treatment of diabetic patients planning a pregnancy. We also discuss the major causes of failure to achieve an optimal management of thyroid dysfunction in diabetic patients and provide recommendations for assessing and treating these disorders during therapy with antidiabetic drugs. An algorithm for a correct approach of these disorders when linked is also provided.

1. Introduction

Diabetes mellitus (DM) rates have reached endemic levels, which is a major challenge for the modern health care system. The presence of other comorbidities drastically affects DM patient outcomes, treatment, and management options. Today, there are 463 million registered patients with this disease in the world, and

by 2030 their number could reach 578 million. The vast majority are patients with type 2 diabetes mellitus (T2DM) (about 90%) [1- 5]. If left untreated, it can lead to frequent hospitalizations and premature death. Diabetes and its complications are among the top 10 causes of death in the world. Most patients with T2DM have at least one complication [6- 10]. Dysfunction of the thyroid gland, after DM, is the second most common metabolic dysfunction in the world [11]. In recent years, researchers have paid more attention to the comorbid course of T2DM with thyroid dysfunction. Among patients with T2DM, thyroid dysfunction is more common than in the general population. The prevalence of thyroid dysfunction among patients with T2DM has been reported to range from 2.2 to 17.0% [12], [13].

Hypothyroidism (HT) and diffuse nontoxic goiter (DNG) are common thyroid pathologies. In regions with sufficient iodine intake, the prevalence of primary HT ranges from 1.0 to 2.0% [14]. On the other hand, in patients with T2DM, according to various authors, the prevalence of HT ranges from 5.7 to 37.1% [15- 17]. The prevalence of DNG increases with increasing iodine deficiency and becomes endemic in populations where iodine intake is insufficient [18]. Thus, in the world population, the prevalence is 15.8%, ranging from 4.7% in America to 28.3% in Africa [19]. The main risk factors for the emergence of DNG are age, sex, hereditary history, iodine levels in household salt, and socio-economic conditions [20- 23]. Recently, researchers have increasingly focused on the relationship between insulin resistance (IR), which is a hallmark of T2DM, and abnormal thyroid function and morphology. The aim of our study was to analyze routine laboratory data of type 2 diabetic patients with thyroid dysfunction and search for possible markers of comorbid course of T2DM, hypothyroidism, and DNG.

2. Patients and Methods

Whereas NAFLD can be diagnosed by imaging studies such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI), the presence of NASH still requires a liver biopsy to identify the presence and location of its features such as inflammation, hepatocyte ballooning, Mallory-Denk bodies, and early fibrosis [13]. Because of the invasive nature and cost of a biopsy, non-invasive means of detecting NASH and various stages of liver fibrosis are sorely needed. A study measuring specific serum metabolites identified by mass spectrometry plus the presence of elevated AST, fasting insulin and the PNPLA3 genotype was found to be good at discerning NASH from NAFL in a northern European cohort [14]. NASH is primarily a disorder of fat metabolism and thus serum lipidomic studies may offer the best opportunity to find specific lipids in the blood that can distinguish NASH from NAFL. Using a purely lipidomic approach, Loomba and colleagues found specific oxidized arachidonic acid species that robustly differentiated NASH from NAFL in a small but extensively characterized cohort in the US [15]. Non-invasively assessing fibrosis is the other major unmet need in NASH diagnostics. A large number of algorithms based on clinical data and imaging to assess fibrosis have been developed, but their major strength tends to be in identifying advanced fibrosis with less utility in earlier stages [16- 19]. A newer technique takes a different approach by looking at collagen turnover using stable isotope labeling of new collagen [20], a technique that may have promise in treatment trials where current histological, serum and instrument based testing lack sensitivity for small changes over short time periods.

3. Results

Lifestyle modification with a focus on healthy eating, weight loss when needed, and regular exercise remain the cornerstone of therapy in adults [28- 31] and children [32]. When recommending healthy food choices, a Mediterranean diet has been shown to be a good alternative to a western diet [13], [33]. Bariatric surgery can be a good option in selected patients and a long term follow up study has been shown to reverse NASH and even substantial fibrosis in some [34], [35]. However, surgery is possible in only a minority of patients and there is clearly a need for pharmacological therapy [36], [37]. Prior clinical trial data suggest that

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pioglitazone or vitamin E may be beneficial in non-diabetic NASH patients [38] and the benefit of pioglitazone on reversing NASH and improving fibrosis was recently confirmed in diabetic patients [39]. More recent trial results are reviewed below and the substrate overload lipotoxic liver injury (SOLLI) model of NASH pathogenesis provides an organized approach to understanding these multiple potential points of attack (Fig. 2). There are no approved drugs for NASH but recent trial data suggests that different approaches may be beneficial in subgroups of patients with NASH. It probably makes sense that no single therapy will reverse NASH in all patients since different patients likely manifest the phenotype of NASH in response to different genetic predispositions and environmental exposures. In addition, a major challenge for taking potential treatments through to approval by government agencies has been identifying meaningful trial endpoints. The field has moved forward due to the combined efforts to address these issues by regulatory agencies, industry, and academics [40].

4. Discussion

The facial nerve canal begins to develop as a narrow groove or sulcus within the cartilage of the otic capsule. Ossification then starts from the apical otic ossification center at 21 gestational weeks and from the canalicular ossification center at 26 gestational weeks near the stapedius muscle. The two centers fuse near the region of the oval window until one year after birth [2], [12]. From an anatomical and radiological standpoint, the facial canal is completely developed by four years of age [13]. However, middle ear inflammations can affect the development of the facial canal in children [12]. Also, facial canal dehiscence may develop due to prior ear surgery, trauma and the pressure effect from tumorous lesions [2]. The incidence of facial canal dehiscence was reported in a relatively wide range from 0.5% [5] to 74% [6] based on histologic and surgical studies. Dehiscence of the facial canal must be at least 1 mm in size to be detected during surgery [12]. However, the incidence of facial canal dehiscence is higher in histological studies, since it can be detected in microdehiscences of less than 1 mm in cadaveric studies [2]. Takashi and Sando found that 40% of all dehiscences were detected on the inferior to inferomedial aspect of the facial canal in the posterior half of the oval window area [6]. Baxter revealed that 85% of all dehiscences occurred through the inferior surface of the tympanic segment toward the oval window niche [14]. In fact, it is not possible to see these dehiscent areas with routine otologic surgery.

5. Conclusions

As we enter an era of increasing genomic, lipidomic and metabolomic information, the future is bright for improving our understanding of the pathogenesis of NASH to the point where we can provide individualized treatment. A challenge in the field now is to correlate the emerging data with treatment responses to attain this goal.

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