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Review Article

Lipidic Classes Involved in Diabetes Mellitus, Review

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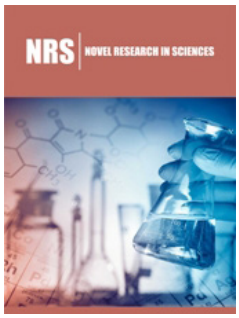

Abstract

Diabetes mellitus is a metabolic disorder of multiple etiology, characterized by an increase in blood sugar concentration (hyperglycemia) and impaired glucose metabolism either as a result of decreased insulin secretion or due to decreased cells sensitivity to insulin. It is classified into two broad categories that do not concern the type of treatment or age but the etiology: Type 1 diabetes (autoimmune, idiopathic) is a disorder in which pancreas does not produce enough insulin. Type 2 diabetes mellitus (disorders of insulin secretion or action) is characterized by a disturbance in the action of insulin (insulin resistance) although the pancreas may produce increased amounts of insulin. Dyslipidemia is one of the main cardiovascular risk factors in diabetic patients. These patients show a specific dyslipidemic profile which is characterized by elevated triglyceride levels, normal or mildly elevated Low-Density Lipoprotein (LDL-C) cholesterol levels and low High-Density Lipoprotein (HDL-C) cholesterol levels. This review presents the main classes of lipids involved in the pathogenesis of Diabetes mellitus, which are triglycerides, phospholipids, and steroids.

Keywords: Diabetes mellitus; Dyslipidemia; Triglycerides; Phospholipids; Steroids

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Lipidic Classes Involved in Diabetes Mellitus

Triglycerides

Triglycerides are the most abundant lipids in human adipose tissue and a major component of Very-Low-Density Lipoprotein (VLDL). According to National Cholesterol Education Program (NCEP) guidelines the desirable triglyceride level is below 150mg/dL [1]. According to the American Diabetes Association (ADA) the most common pattern of dyslipidemia in patients with type 2 diabetes is elevated triglyceride levels and decreased HDL cholesterol levels [2]. The condition in which triglyceride levels are elevated is called hypertriglyceridemia and can be classified into mild to moderate (triglycerides between 150-499mg/dL) and severe hypertriglyceridemia (triglycerides ≥500mg/dL) [3]. Triglyceride values over 1,000mg/dL are accompanied by a serious risk of acute pancreatitis. In a retrospective cohort-based study with 1,586 patients with diabetes type 2 the prevalence of pancreatitis was 3.7% [4]. Several clinical studies [5-10] have demonstrated that elevated blood triglyceride levels increase the risk of Type 2 Diabetes (T2D). It is well recognized that diabetes is a risk factor for cardiovascular disease and has been associated with 2- to 4-fold higher mortality [11] which is mainly due to atherogenic dyslipidemias characterized, among other factors, by elevated levels of triglycerides [12].

Recent randomization studies have demonstrated that hypertriglyceridemia is a causative agent in atherosclerosis [13,14]. The main step in order to reduce the risk of cardiovascular diseases related with diabetes is the detection and treatment of dyslipidemia which include the reduction of triglyceride levels. A study showed significant hypertriglyceridemia in all

diabetic patients irrespective of the duration of diabetes and a significant negative correlation between triglyceride levels and heart rate variability whose reduction is related to increased mortality risk [12]. Hypertriglyceridemia has been characterized as an independent risk factor for diabetes type 2 incidence even after the control of Body Mass Index (BMI), hypertension and all other conventional risk factors [8,15,16]. The triglyceride levels and the triglyceride–HDL cholesterol ratio are important markers for identifying overweight persons who are insulin resistant, and they are in high risk for cardiovascular disease as much as ten years before diagnosis of T2D [17]. Zhao et al. [10] studied the association between triglyceride and diabetes type 2 among healthy middle-aged and older adults in a prospective study with 8-year follow-ups in two cohorts. Their results showed that there was a significant linear association between triglyceride levels and the incidence of diabetes type 2. It is worth noticing that this association was independent of other factors such as age, sex, BMI and hypertension. A retrospective longitudinal study [5] which evaluated the risk of diabetes and prediabetes in the presence of a wide spectrum of triglyceride levels was carried out employing data from a screening center between the years 2000 and 2012. None of the study participants had evidence of diabetes while they had fasting plasma triglyceride level of 24-1130mg/dL at their initial visit. The results showed that every 10mg/dL increase in triglyceride levels increased the risk of diabetes by 4%. It is impressive that this association is valid even when the sustained increments in serum triglycerides level remained within the accepted normal range. Dotevall et al. [8] demonstrated that for middle-aged women without prior diabetes or cardiovascular disease, even very slightly elevated triglycerides levels resulted in significantly increased risk of developing diabetes regardless of age, BMI, blood pressure and physical activity. A very large population multicenter cross-sectional study [18] conducted between 2011 to 2013 in patients with type 2 diabetes showed that elevated triglyceride levels was the strongest factor among those associated with inadequate glycemic control in patients treated with sufficient dose of insulin and/or oral antidiabetic drugs. Due to the significant increase in prevalence of type 2 diabetes which is expected in developing countries between 2010 and 2030 [19], it is very important to identify individuals who have higher risks for diabetes in order to ensure early prevention and treatment.

Phospholipids

Phospholipids are a class a of lipids which represent the major component of the bilayer of the cell membrane and their structure consists of two major parts [20,21]. Two hydrophobic fatty acids “tails” and a hydrophilic “head” comprise a phosphate group. Phospholipids may also be divided into two groups through differences in their backbones, the one group, the glycerol-based phospholipids (glycerophospholipids) consists of phosphate groups which are modified with simple organic molecules such as choline (to form phosphatidylcholine), ethanolamine (to form phosphatidylethanolamine), inositol (to form phosphatidylinositol), serine (to form phosphatidylserine) or two phosphatidic acid moieties connected with a glycerol backbone in the centre to form cardiolipin. The other group contains the backbone of a sphingosine base, the sphingolipids [22]. Only sphingomyelin, which contains a phosphate group, belongs to this group of phospholipids. In mammalian cells, de novo synthesis of glycerophospholipids requires the acquisition of diacylglycerol units obtained through either diacylglycerol or Cytidine Diphosphate-Diacylglycerol (CDP-DAG) synthesized from phosphatidic acid [23,24].

Insulin resistance is the most common pathological factor accompanied by obesity which can be observed in patients suffering from diabetes type 2. The presence of insulin resistance in insulin-sensitive target tissues results in abnormalities such as hyperglycaemia, hyperinsulinemia, and hypertriglyceridemia, common features of the metabolic syndrome [25,26]. For decades, high triacylglycerol and cholesterol levels were considered to be the cause of these metabolic abnormalities, although recent studies have proposed that in addition to the raised triacylglycerol and cholesterol levels, phospholipid alterations could possibly play a role in metabolic disorders [27-30]. Decreased insulin sensitivity associated with decreased concentration of Polyunsaturated Fatty Acids (PUFA) in skeletal muscle phospholipids has been observed in clinical studies, which implies that changes in the fatty acid composition of the cell membranes could possibly affect the action of insulin [31]. A study conducted in older adults showed a positive relationship between the proportion of palmitic acid (C16:0) in the skeletal muscle phospholipids and the insulin sensitivity index [32]. This association was newly confirmed but it was also observed that the fatty acid composition of phosphatidylcholine and not phosphatidylethanolamine from skeletal muscle membranes was of importance in this association [33]. In that study, healthy patients were treated with nicotinic acid, an agent known to induce insulin resistance in humans. Treatment with nicotinic acid was associated with a 25% increase in the half-maximal insulin concentration and decreased peripheral insulin sensitivity, and this was accompanied by significant increase in the phosphatidylcholine (C16:0), decrease phosphatidylcholine (C18:0) and long-chain n-3 fatty acid and PUFA. Recently, a clinical study in elderly participants also showed an association between decreased odds of abnormal homoeostasis model assessment-insulin resistance (HOMA-IR) and some phosphatidylcholine species (C32:0, C32:1, C32:2, C34:1, C34:2, C34:3, C36:2, C36:3, C40:5, C40:6, C42:3, C42:4 and C42:5) [34]. Furthermore, changes in the total content of phosphatidylcholine or phosphatidylethanolamine are also associated with insulin insensitivity. A clinical study conducted in lean control and overweight but non-diabetic patients showed that baseline fasting plasma insulin and HOMA-IR were positively correlated with erythrocyte membrane phosphatidylethanolamine and phosphatidylcholine content in the whole population [28]. Glycerolphospholipids, such as cardiolipin and phosphatidylinositol derivatives, have been shown to be associated with insulin sensitivity in clinical studies [35,36]. Cardiolipin content was increased by daily moderate-intensity exercise in type 2 diabetic patients, and this was accompanied by improved insulin sensitivity [36]. Interestingly, obese patients with weight loss through gastric bypass surgery showed changes in only specific fatty acid species of cardiolipin

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after exercise without significant changes in total cardiolipin content [37]. Although the association between phospholipids and insulin sensitivity has been shown through clinical studies, it is not yet clarified whether changes in phospholipids are the cause or the consequence of insulin resistance.

Platelet activating factor: The Platelet Activating Factor (Platelet Activating Factor, PAF) is a lipoid which belongs to the class of phospholipids. Its name is: 1-O-alkyl-2-acetyl-sn-glycerol-3-phospho-choline and Figure 1 [38]. PAF biosynthesis occurs through remodeling and de novo pathway. De novo pathway is believed to be responsible for PAF continuous production in blood and various tissues. Central enzyme in this process is alkyl acetylglycerol phosphocholino transferase (PAFCPT). Remodeling pathway is believed to be responsible for PAF production in inflammatory situations. Central enzyme is lyso- PAF: acetyl-CoA acetyltransferase (lyso-PAF-AT). Regarding PAF catabolism, the most important enzyme involved is PAF-acetylhydrolase (PAF-AH) which hydrolyzes short chain acyl groups from sn-2 position of PAF and forms lyso-PAF. PAF through its connection to one well-marked receptor starts proliferation actions in pre-inflammatory cells involved in pathology of most chronic diseases, including cardiovascular and renal diseases, diabetes, central nervous system CNS diseases and cancer.

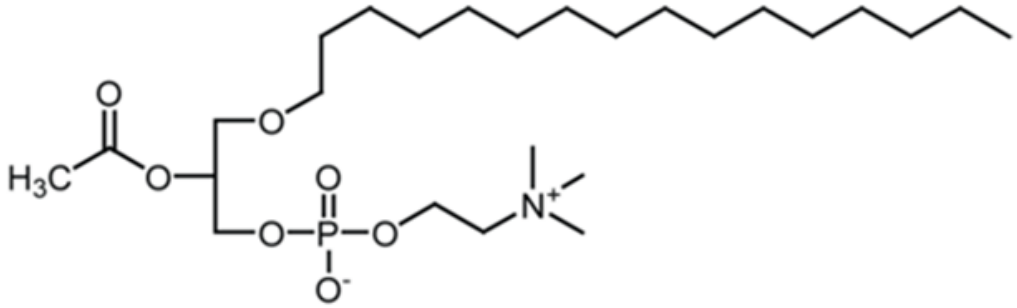

Figure 1: PAF structure.

Inflammatory processes contribute significantly to the initiation, progression and rupture of lipid-rich atherosclerotic plaques. Atherogenic lipoproteins, including VLDL, VLDL remnants, IDL, LDL and Lp(a) are enhanced in atherogenic dyslipidemias such as hypercholesterolemia (Type IIA), mixed hyperlipidemia (Type IIB), and the dyslipidemia of Type II diabetes. The main points of atherogenesis mechanism due to PAF involvement is increase in blood levels, decreased levels of antioxidants molecules and PAF-AH activity [39]. PAF like derivatives and oxidized phospholipids OxPLs, have been identified in atherosclerotic plaque. PAF-like molecules are formed when cell membrane is oxidized, resulting in compounds with smaller peroxidized residues on the second carbon which mimic PAF action. PAF-AH decomposes pro-inflammatory OxPLs and has a main role in lysophosphatidylcholine (lyso-PC) and oxidized fatty acids formation, many of which have inflammatory properties [39-41]. PAF like molecules and other vasoactive metabolites such as arachidonic acid, histamine, cytokines, chemokines and proteolytic enzymes can be released from mast cells during atherosclerotic plaque formation and cause hypercholesterolemia and hyperglycemia [42]. PAF role as an inflammatory mediator in pathogenesis of diabetes has been also studied. PAF levels are statistically increased in serum of diabetic patients while PAF levels in pancreas homogenates of three different groups of animals: well-fed, STZ-induced diabetic and fasted rats are elevated in diabetic animals [43,44]. PAF levels are also increased in plasma of pregnant women affected by Gestational Diabetes Mellitus (GDM), connecting inflammation, oxidative stress, and metabolic results [45] while PAF-AH shows a higher activity in patients with type 1 diabetes, which may be related to the higher risk of developing cardiovascular diseases observed in these patients [46].

Steroids

From the end of the last century, western societies have observed a notable increase of metabolic disorders including dyslipidemia, insulin resistance, hypertension, overweight and obesity [47], that will inevitably result in unprecedentedly high incidences of type 2 diabetes and cardiovascular disease worldwide [19,48]. For this reason, medical and scientific community has realized numerous studies on metabolic disorders focusing on steroid hormones, due to their fundamental role in the etiology and pathogenesis of metabolic disorders including obesity, diabetes and insulin resistance [49]. It is well known that glucocorticoids are extensively used in medicine either in short-term acute steroid therapy (exacerbation of chronic obstructive pulmonary disease, acute gout, chemotherapy protocols, bacterial meningitis and in pregnant women for fetal lung maturation, etc.) or in chronic-term steroid therapy in several diseases (pulmonary diseases, autoimmune conditions, neurologic diseases, inflammatory bowel diseases) as well as in modulating the immune system following solid organ transplantation. Although glucocorticoids are widely known in all medical specialties for their anti-inflammatory and immunosuppressive properties, they have various common metabolic side effects including hypertension, osteoporosis and diabetes. Specifically, for over 50 years, Steroid-Induced Diabetes Mellitus (SIDM) has been recognized as a complication of glucocorticoid use due to various reasons (impairment of multiple pathways including beta cell dysfunction, insulin resistance

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in other tissue, glucocorticoids effect on glyceroneogenesis in liver and adipose tissue). Diagnosing impaired fasting glucose or impaired glucose tolerance prior to the initiation of chronic glucocorticoids will better identify those who would benefit from steroid-sparing treatment, or if this is not an option, blood glucose monitoring while starting therapy. Further investigation into the precise mechanism of steroid-induced insulin resistance as well as exploring dose titration of insulin in patients on glucocorticoids possibly utilizing technology like continuous glucose monitoring system will provide insight into future diabetes prevention efforts and targeted therapies. It should be noted that as with all types of diabetes, initial steps to improve glycemic control include lifestyle modification (exercise and dietary counselling) to provide options that can perhaps lessen post-prandial hyperglycemia, but the mainstay of treatment is insulin therapy coincident with meals [50].

In addition, peripheral glucocorticoid metabolism through the promising avenue of selective 11_- hydroxysteroid dehydrogenase type 1 (11_-HSD1) inhibitors [51] as well as dysregulation of corticosteroid hormone production affect all metabolic diseases including obesity and insulin resistance. Whilst glucocorticoids have a potent impact upon metabolic phenotype, sex steroids (estrogens, estradiol) and physical activity play an equally important role in metabolic homeostasis [52-54].

Conclusion

it should be noted the potential risk of hyperglycemia in patients with diabetes following intra-articular steroid injections, that are widely used for the symptomatic control of degenerative and inflammatory joint arthritis. The benefits of steroids are due to their anti-inflammatory effects, as it has been already indicated. Locally injected steroids have been shown to be absorbed into the systemic circulation, affect glucose metabolism and can cause abnormal blood glucose levels in patients with diabetes. For this reason, patients with diabetes following intra-articular steroid injections need regular monitoring of blood glucose levels after injection for up to a week after injection, while they should seek medical advice if safe thresholds are breached [55].

Author Contributions

Conceptualization, MT; investigation, AB, EK and AP; writing-original draft preparation, AB, EK, DZL and AP; writing-review and editing, DZL; supervision, MT; project administration, MT. All authors have read and agreed to the published version of the manuscript.

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