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Hypogonadism and NAFLD in diabetic male patients

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Background

Diabetes mellitus (DM) is a complex chronic illness associated with a state of high blood glucose level, or hyperglycemia, occurring from deficiencies in insulin secretion, action, or both. The chronic metabolic imbalance associated with this disease puts patients at high risk for long-term macro- and microvascular complications(1).Development of type 2 DM is multifactorial genetic, environmental and behavioral(1).

Metabolic syndrome represents a cluster of related metabolic abnormalities, including central obesity, hypertension, dyslipidemia, hyperglycemia, and insulin resistance, with central obesity and insulin resistance in particular recognized as causative factor(2).

It has been confirmed that male patients with type 2 diabetes are significantly more likely to develop hypogonadism: the proportions of diabetes patients with low total testosterone (TT) levels are 36.5%(3).

Male hypogonadism is a common disease characterized by certain clinical features and low levels of serum testosterone Its typical clinical manifestations include physical decline, memory loss, difficulty paying attention, depression, loss of libido, and erectile dysfunction. It significantly impacts patients' quality of life (4).

The serum total testosterone level is regarded as the most reliable indicator of hypogonadism. The International Society of Andrology recommends that hypogonadism be diagnosed if TT levels are below 12 nmol/L in males (5). it seems that there is a vicious cycle in terms that visceral obesity could cause androgen deficiency and androgen deficiency could lead, in turn, to obesity, insulin resistance and metabolic syndrome.it has been suggested that T inhibits the uptake of triglycerides and facilitates lipid mobilization from visceral fat, thus being inversely associated with visceral fat mass(6).

NAFLD is considered to be the hepatic component of the metabolic syndrome (MetS) and is associated with increased visceral adipose tissue (VAT) and insulin resistance and its global prevalence of NAFLD continues to rise in conjunction with rapid increases in rates of obesity and diabetes in recent years(7).

Non-alcoholic fatty liver disease (NAFLD) refers to a condition where there is an excess buildup of triglycerides in the liver parenchyma in the absence of excess alcohol consumption (5). NAFLD course has four clinical-pathological entities: steatosis, NASH, advanced fibrosis/cirrhosis, and HCC.

Most patients with NAFLD will have simple steatosis, (fatty changes affecting >5% of hepatocytes), usually associated with mildchronic inflammation(8).

The human liver expresses estrogen and androgen receptors, although at a lower degree comparing to reproductive organs, a fact that implies the importance of sex steroids in liver energy metabolism and homeostasis(9,10). The pathogenesis of NAFLD is a multi-factorial disease resulting from a complex interaction of environmental "hits" and a genetic background(11). Development and progression of NAFLD are strongly associated with insulin resistance (IR) and metabolic syndrome (MetS) components, particularly abdominal obesity and T2DM(11).

Since insulin suppresses lipolysis in adipose tissue, in a state of insulin resistance, there is an increased influx of fatty acids to the liver(12). there has been speculation that free fatty acids

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themselves can directly cause injury to the liver as they undergo esterification with glycerol to form triglycerides in hepatocytes and activate an inflammatory pathway(12).

accumulation of triglycerides and free fatty acids in the hepatic parenchyma due to an imbalance between the influx and synthesis of lipids and the export and β-oxidation of lipids makes the liver susceptible to injury caused by inflammation, adipokines, gut-derived endotoxins, mitochondrial dysfunction, and oxidative stress(7).

There are studies have been demonstrated that low serum testosterone level is independent factor for NAFLD(13, 14, 15, 16). and it has been demonstrated that T administration result in decrease in liver enzyme concentrations and has favorable effect in regard to visceral fat accumulation and other elements of metabolic syndrome(17, 18).

Liver injury with fatty acids and accumulation of triglycerides in hepatocytes lead to activation of an inflammatory pathway(12).

Along with liver-resident cells, monocytes and monocyte-derived macrophages participate in the response to both tissue injury and infection(19).

innate myeloid cells—including neutrophils and monocytes—are rapidly recruited to the site of injury (20).

The precise role that monocytes play in the response to insult is an area of active research involving questions such as: What types of monocytes are recruited?, Do monocytes contribute to initial injury and development of fibrosis or do monocytes contribute to the termination of injury and the regression of fibrosis? (19).

There are three monocyte subsets ("classical" CD14++ CD16-, "intermediate" CD14++ CD16+, "nonclassical" CD14+CD16++monocytes). It was revealed that the nonclassical monocyte fraction, total monocyte fraction and count were increased in NAFLD, while classical monocyte fraction was decreased. Total monocyte fraction, nonclassical monocyte fraction, and waist circumstance were independent risk factors for NAFLD (20), so it is suggested that nonclassical monocyte fraction and total monocyte fraction might have potential as a prognostic and modifiable biomarker in NFALD patients. This novel marker set might therefore be of interest to monitor inflammatory pathways in individuals with hepatic manifestation of the metabolic syndrome (21).

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