Central Obesity and the Consequences of Metabolic Syndrome

Subjects: Clinical Neurology
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Central obesity refers to excessive abdominal fat that builds up around visceral organs and negatively impacts health. It is the key element of the MetS, the common pathological feature in diabetes and cardiovascular disease. Central obesity has more important health consequences than the body mass index in general and the CTS in particular. Apparently, central androgenic obesity does not fit the female predominance of the CTS. This gender distribution was initially explained by the smaller cross-sectional area of the carpal tunnel in women and the fluid retention caused by estrogens.

obesity carpal tunnel syndrome metabolic syndrome central obesity myosteatosis

1. Introduction

The visceral deposition of the adipose tissue has major implications on insulin resistance. Related to the etiopathology of the CTS, insulin resistance directly affects the peripheral nervous system and indirectly through the vascular and muscle and tendons impairment (**Figure 1**).

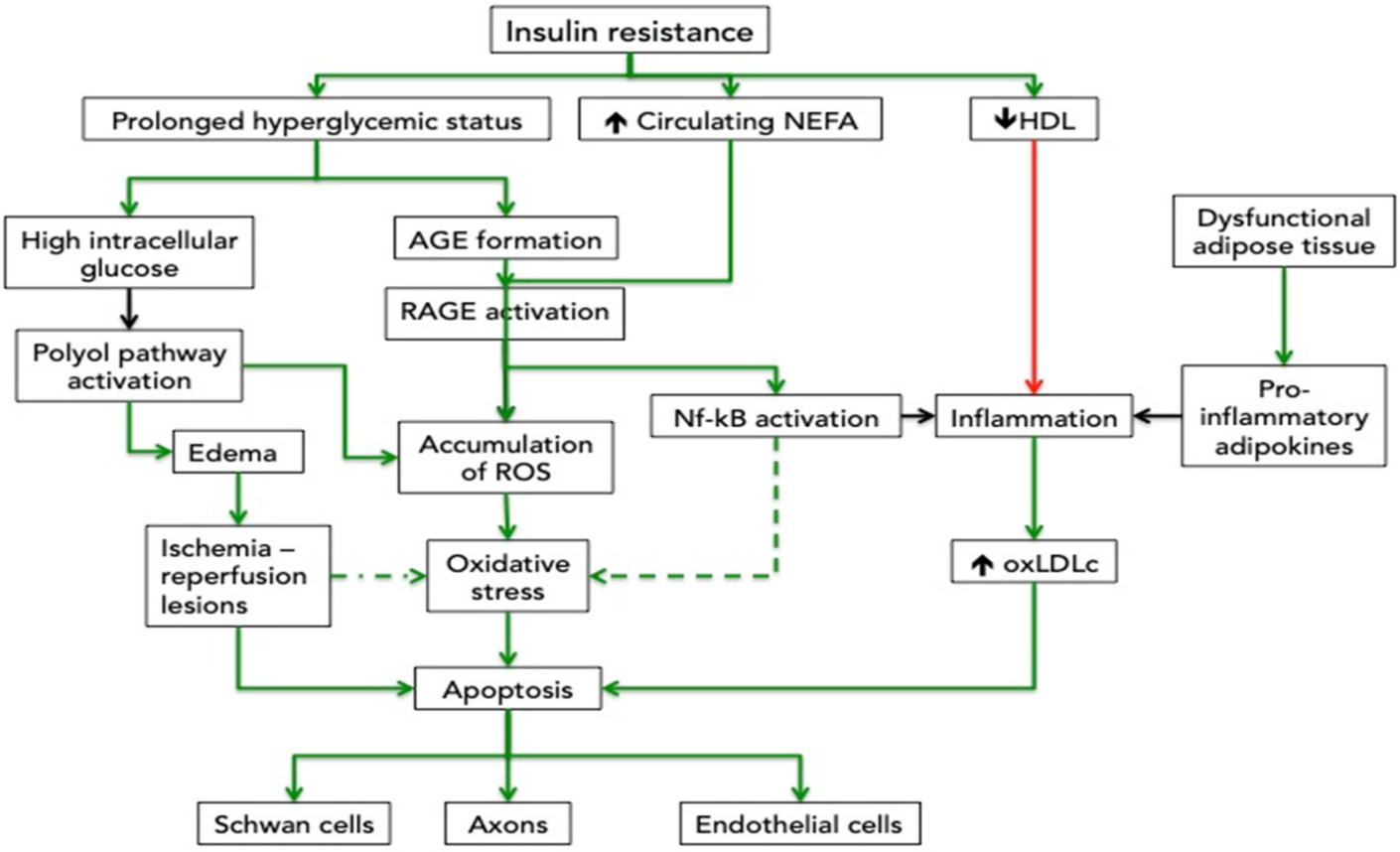

Figure 1. Insulin resistance and polyneuropathy. Insulin resistance is characterized by hyperglycemia, increased non-esterified fatty acid (NEFA) and dyslipidemia (low circulating HDL particles and high LDL). At cellular levels, the oxidative stress and the inflammation contribute to the destruction of Schwann cells, axons and endothelial cells. AGE= advanced glycation end products; HDL = high density lipoprotein; oxLDLc = oxidized low density lipoprotein; NEFA = non esterified fatty acids; Nf-kB = nuclear factor kappa B; RAGE = receptors for advanced glycation end products; ROS= reactive oxygen species; Green line = direct effect; red line = inhibition.

2. Effects of Hyperglycemia on Nerve Impairment

The presence of the MetS almost doubles the chance of peripheral neuropathy [1]. In this study, the relation between MetS and neuropathy was independent of the presence of diabetes but closely related to the waist circumference and triglyceridemia. Thus, searching for and correcting of the MetS components, was proposed for any idiopathic neuropathy [2].

Some researchers found that peripheral neuropathy was only associated with insulin resistance being independent of the MetS [3]. An indirect proof of a long subclinical evolution of neuropathy is the finding of a reduced sensory nerve action potential amplitude in the median nerve in 70% of patients on the first diagnosis of type 2 diabetes mellitus (T2DM) [4].

The neuropathy induced by hyperglycemia combines axonopathy with Schwannopathy features. The decrease in the Na+-K+ pump activity alters the axonal function [5]. The reduced trans-axonal ionic gradient and ionic currents

influence neuronal transmission and conduction velocity. The Schwann cells' dysfunction is responsible for the morphological changes in the myelin sheath, the disruption of the neural support, and the impaired repair of damaged nerves [6].

Several mechanisms explain these modifications. The high intracellular glucose activates other catabolic processes than glycolysis, such as the polyol pathway. The polyol pathway starts with the transformation of glucose into sorbitol, catalyzed by aldolase reductase. This reaction utilizes a hydrogen group donated by NADPH. Sorbitol is then converted into fructose via sorbitol dehydrogenase and donates a hydrogen group to NAD+, maintaining the redox balance. The second reaction does not occur in cells missing sorbitol dehydrogenase, such as the Schwann cells [7]. As a consequence, these cells will acquire an unbalanced NADPH/NAD equilibrium and accumulate reactive oxygen species (ROS). These supplementary ROS are added to the already existing high level of ROS produced by the mitochondria exposed to high levels of intracellular glucose and as well as by the activation of the RAGE inside the neurons. The first organelles damaged by ROS are the mithocondria. Therefore, the axons, which have a large mitochondrial pool and depend on the local energy production, are the neuron parts mostly susceptible to the ROS effects [8]. Besides the oxidative stress, sorbitol is an osmotic compound that attracts water into the cell and produces cellular edema. It has been shown that the activation of the polyol pathway induces oxidative stress, edema, and de-differentiate de Schwann cells, a process which is reversed by an inhibitor of the sorbitol formation [9].

3. Effects of Dyslipidemia on Nerve Impairment

There is also a significant contribution of dyslipidemia to peripheral nerves deterioration, even if the clinical association is less consistent. Some authors found an association between hypertriglyceridemia and subclinical motor and sensory axonopathy, expressed by the delay in distal latencies and decrease in conduction velocities [10] [11]. Others have found this association only in those with uncontrolled glycemia or did not find any relation with triglycerides (TG) [12][13]. A systematic review concluded that the association is, however, valid in the subgroup of T2DM [14].

These apparently conflicting results might reflect the independent analysis of the one-by-one components (e.g. TG) of the complex lipid transport system in disregard of the dynamic exchange in lipid content between the lipoprotein particles and the direct and reverse cholesterol movement. TG is an important marker of how much cholesterol is delivered to the peripheral cells but should be considered in relation to the activity of cholesteryl-ester transfer protein, which transfers TG and cholesterol esters to LDL particles, or with the activity of the lipoprotein lipase, which transforms the TG rich LDL particles in small-LDL particles [15]. The reverse transport should be taken into account as well, particularly for the low HDL-c in MetS. Experimental data show that reduction of TG and of the non-esterified fatty acid (NEFA) without normalization of glycemia are able to ameliorate the peripheral neuropathy [16]. Even more, the high level of circulation NEFA increase the superoxide production in human Schwann and endothelial cells [17]. The glycated albumin, which is more abundant in insulin resistance states, facilitates the NEFA penetration of the blood-nerve barrier [18].

The HDL molecule, which is generally in lower concentrations in plasma from patients with MetS, is not only the carrier for reverse cholesterol transport, but has also anti-inflammatory and antioxidant properties [19]. In fact, systemic low-grade inflammation is a characteristic of the MetS and is mainly part of the abnormal secretory pattern of the “unhealthy” adipocytes.

In the inflammatory context of the MetS, the small low-density lipoprotein cholesterol (LDL-C) is more frequently oxidized [20]. Besides the well-known effects on endothelium, the oxidized LDL (oxLDL) could also link to the oxLDL receptor in neurons. During periods of high-fat diet-induced dyslipidemia, the oxLDL receptor in the dorsal root ganglia neurons of mice is activated and contributes to oxidative stress. Even more, in this experiment, the oxLDL effect was additive to the one derived from the hyperglycemic status [21]. The oxidative milieu favors the formation of oxysterols from cholesterol. The oxysterols induce the caspase 8 pathway and apoptosis of the neurons [22].

Peripheral neurons also express the liver X receptors (LXR α/β) (NR1H3 and NR1H2), a cholesterol sensor that works as a transcription factor to control the lipid metabolism [23]. Gavini et al showed that the LXR reduces the proliferation of the Schwan cells in obesity. The effect was directly related to the downregulation of neurogenic 1 by saturated fatty acids [24]. The same group found also that activation of LXR can reduce pain in diet-induced obesity. In the presence of a powerful agonist of LXR, the lipid content of the macrophages from peripheral nerves was reduced with a consequent decline in inflammation and the slower progression of the nerve lesions [25]. All the above, suggest that LXR could explain symptoms of obesity associated CTS, and should be investigated for their therapeutically potential.

Confounder in the relation between dyslipidemia and CTS that must be taken into account in epidemiological studies is hypothyroidism, as on one side, CTS is more frequent in patients with this medical condition and on the other side dyslipdemia, hyperinsulinemia and large waist circumference are present even in mild hypothyroidism [26]. In some studies, the body mass index (BMI) was the link between hypothyroidism and CTS [27][28]. Even in euthyroidism, the TSH level in the upper range significantly increases the chances of MetS [29].

The thyroid hormones are essential for the lipid metabolism. In hypothyroidism, there is an imbalance between cholesterol synthesis and clearance. There are at least thre mechanisms by which the clearance of the LDL is reduced: the diminished synthesis of the LDL-receptor, decreased hepatic cholesterol uptake, and biliary excretion [30]. On the other side, the oxidation of the LDL-receptor increases favors inflammation and oxidative stress [24]. The lipoprotein lipase activity is also impaired in hypothyroidism, because it reduces the TG clearance and increases the circulating VLDL particles [31]. The synthesis of the endogenous cholesterol is not increased while the amount of available cholesterol in the liver is maintained or even made higher because the cholesterol absorption increases and the beta-oxidation in hepatocytes decreases; the overall effect is a higher VLDL output from the liver [32]. TSH increases the activity of the hormone-sensitive lipase and the adipocyte lipolysis, mobilizing more fatty acids in the circulation [33]. The HDL synthesis and maturation are also affected, as the thyroid hormones favor the synthesis of apoA1 and the efflux of cholesterol from macrophages via the ATP-binding cassette A1 [34]. Overall, hypothyroidism increases TG, LDL, and VLDL and reduces the reverse transport and the excretion of cholesterol [35]. To the general effects of dislipidemia on the peripheral nerves, hypothyroidism adds the deposition

of pseudo mucinous substances on the median nerve sheath and the decrease in the cross-sectional area of the carpal tunnel [28][36]. The latest effect was reversed by thyroxin treatment.

Fat is also a deposit for neurotoxic occupational hazards and accumulation of these toxicants might delay their excretion. One of the best characterized peripheral neurotoxic with adipose tissue tropism is n-hexane [37]. The chronic n-hexane exposure initiates the formation of lysine adducts with cytoskeletal proteins; the changes in the protein structure interfere with the insertion of newly synthesized neurofilaments into the axonal cytoskeleton and the microtubule-binding and leads to the atrophy of the nerve, sensory and motor impairment [38][39].

Taken together, these general neural dysfunction mechanisms could be included in the expanded understanding of the double crash syndrome, defined as the coexistence of a local compression with a systemic cause of neuropathy [40].

4. Vascular effects

The median nerve is affected by ischemia, secondary to the vascular remodeling or through compression of the nerve inside an abnormal narrow tunnel. Both mechanisms might be the consequences of vascular modifications which characterize the MetS.

The microcirculation dysfunction is a well-known effect of T2DM and the high prevalence of the subclinical neuropathy on diagnosis is a solid argument for the deleterious effects of the long-term preexisting insulin resistance.

Inside the endothelial cells, the insulin resistance generates an imbalance between the phosphatidylinositol-3-kinase (PI3-k) and the mitogen-activated protein kinase (MAPK) pathways which results in impaired vasodilatation, a procoagulant status, the NADPH-oxidase activation, and ROS production, smooth muscle cells proliferation, augmented response to catecholamines and endothelial dysfunction [41][42][43]. In CTS, the arteriolosclerosis of the small arteries of flexor tenosynovium was observed. The narrowing of the arteriolar lumen was due to the intimal hyperplasia related to the higher expression of matrix-metalloproteinases 2 (MMP-2) [44]. A similar vascular remodeling can be induced by insulin resistance. It has been demonstrated that diet-induced insulin resistance in rats increases MMP-2 arteriolar activity, a process which was reversed by doxycycline, a blocker of the activity site of MMP-2 [45].

In a hyperglycemic status, the advanced glycation end products (AGE) are formed in high amounts, the specific but not the only ligand of the advanced glycation end products receptor (RAGE). Experimental data showed that “advanced oxidation protein products”, food-derived advanced glycated end products, calgranulin, amphoterin, and amyloid-b-peptide released during metabolic or oxidative cellular stress, are also able to activate RAGE. The RAGE-induced signal activates nuclear factor-kB (Nf-KB), the early growth peptide 1, and the NADPH-oxidase and yields oxidative stress, inflammatory and prothrombotic species in atherosclerosis-prone vessels [41].

Hyperglycemia also influences lipid metabolism. The irreversible glycation of the LDL-C enhances its oxidative and inflammatory potential on the vascular cells [46]. Dyslipidemia generated by the enhanced lipolysis in adipocytes and de novo lipid synthesis in the hepatocytes increases the formation of the asymmetrical dimethylarginine (ADMA). ADMA inhibits the NO-synthetase, reducing the formation of nitric oxide (NO) and the vascular homeostasis [47]. Indeed, the ADMA was elevated in plasma from patients with MetS compared to controls [48].

MetS and hypothyroidism also share some common pathological mechanisms referring to vascular impairments such as the abnormal NO and vascular endothelial growth factor (VEGF) production [49]. A meta-analysis showed that VEGF-A is associated with diabetes, while VEGF-B and C are associated with the MetS and its components [50]. In vitro, the VEGF transcription is stimulated by TSH [51]. The members of the VEGF family have pleiotropic effects in vessels; they increase the permeability, which leads to edema and further narrowing of the CT space, stimulate the multiplication of the endothelial cells with intimal thickening, the development of collateral branches and the neovascularization [52] [53]. The neovascularization in sub-synovial connective tissue supports the high proliferation and thickening of the tendon sheet, further contributing to the narrowing of the tunnel which is more pronounced in diabetes CTS than in patients without T2DM [54]. The process seems to be influenced by the polymorphisms of the VEGF gene, as reflected by the more frequent neuropathy in patients with T2DM and D allele of the VEGF gene [55]. Leptin, an adipokine secreted in high levels by the visceral fat, has synergic effects with VEGF, on the capillary fenestration and permeability [56] [57].

The higher incidence of CTS in smokers and the relation with the MetS calls for some specific comments. The odds ratio of CTS in smokers is 4.862 (95% CI, 3.991-5.925) and many studies revealed an association between smoking and central obesity, even if there is no unanimous agreement [58][59][60][61][62]. Both body weight variation and nicotine addiction have genetic components [63][64]. In a large sample of current, former, and never smokers, investigators using the Genome-wide Complex Trait Analysis found a positive relationship between genetic factors influencing the smoking habit and BMI [65]. In this study, common genetic variants predisposing to the intensity of smoking behavior and an increased BMI were identified. The influence of gender on this association is also inconsistent, with studies in which the influence of smoking is predominated in women, and others in which it was restricted only to men [61][66]. Although both smoking and the female sex are well-known risk factors for CTS the interaction of these two is neglected, as it is for other pathologies [67][68]. At least from the biological perspective, prospective studies to capture the potential synergic effect of these risk factors are still needed.

In what concerns the pathological mechanism, smoking has multiple negative effects on the vascular system. Active smokers have thicker arterial walls, lower flow-mediated dilatation, and response to nitroglycerine [69]. Nicotine activates the sympathetic nervous system and the production of ROS and nitrogen species increases lipolysis in white adipose tissue and contributes to insulin resistance in muscle cells [70]. Nicotine also reduces the antioxidant enzymes (superoxide dismutase) and the activity of the endothelial nitric oxide synthase, altering the endothelial function [71]. Experimental data show a slow recovery after an ischemia-reperfusion injury related to smoking. [72]. In healthy non-smokers, a 30 minutes passive exposure to smoking decreases the rate of oxygen consumption and the reperfusion after vascular occlusion and the capillary blood flow is significantly decreased[73] [74]. In experiments conducted on the extensor digitorum longus, the chronic adaptation to hypoxia related to the

blockade of hemoglobin with carbon monoxide and vasoconstriction diminished the volume of the type II muscle fibers and increased the fiber oxidative enzyme activity [75].

The relation between MetS, cardiovascular diseases, and CTS is also endorsed by epidemiological data. Hypertensive patients aged 30-44 from a Finish population-based survey, had an OR of 3.4, (95% CI 1.6-7.4) for CTS; the association with cardiac arrhythmia was even stronger (OR 10.2, 95% CI 2.7-38.4) [76]. The relation between high blood pressure and CTS was maintained after adjustment to gender, BMI, and occupational risk factors, expressed in the strain index [77]. It is also of interest that CTS might predict future risk of coronary heart disease cardiac failure, atrial fibrillation, atrioventricular heart block, and pacemaker implantation [78][79]. Most probably due to the shared risk factors (dyslipidemia, impaired metabolism and inflammation) and the effects of the MetS on the microvascular structure which lead to a reduction in the endoneurial blood flow, oxygenation, and hypoxia of the median nerve.

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