Cigarette smoking/cessation and metabolic syndrome

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ABSTRACT
The metabolic syndrome (MetS) is a common cluster of pre-morbid, modified metabolic-vascular risk factors/diseases (visceral obesity, hyperglycaemia, dyslipidaemia and hypertension) associated with increased cardiovascular (CV) morbidity, fatty liver and risk of cancer. Several studies reported a higher incidence of MetS in smokers. Cigarette smoking plays a substantial role in the pathogenesis of numerous chronic diseases such as CV disease (CVD), cancer, lung disease and others. However, due to the existence of the so-called “smoking paradox”, the impact of this risk factor on CVD mortality is still not clear. Smoking cigarettes may increase risk of MetS or worsen it by numerous mechanisms. Furthermore, individuals who quit smoking tend to increase their body weight. The possibility of gaining weight can stop smokers from quitting and increases the risk of relapse, particularly in women. Herein, we review the cigarette smoking status (active/cessation) in relation to the MetS.

Introduction
The metabolic syndrome (MetS) is a common cluster of pre-morbid, modified metabolic-vascular risk factors/diseases (visceral obesity, hyperglycaemia, dyslipidaemia and hypertension) associated with increased cardiovascular (CV) morbidity, fatty liver, risk of cancer and others.[1] Long before the modern recognition of MetS > 250 years ago, Joannes Baptista Morgagni described the association between visceral obesity, hypertension, hyperuricaemia, atherosclerosis and obstructive sleep apnoea.[5] Also, Kylin, in 1923, reported the correlation between obesity, hyperglycaemia, hypertension and hyperuricaemia.[6] In the same year, Preble [7] evaluated data of 1000 patients (700 from his private clinic and 300 from Boston Hospital) and concluded that overweight is a serious condition, which gradually leads to “heart, arterial and kidney disease, diabetes and hypertension”. He also reported that weight loss reduced blood pressure (BP) and albuminuria. In the 1930s, Himsworth considered insulin resistance (IR) as an important mechanism for diabetes mellitus.[8] After that, Vague [9], evaluated the connection between visceral obesity, dyslipidaemia, glucose intolerance, hyperuricaemia and CV disease (CVD). This condition was later called by Avogaro et al. [10] as plurimetabolic syndrome. Following, obesity was accepted as a motivating process for developing MetS with IR and impaired lipolysis as the main pathophysiology.[11] In 1979, DeFronzo et al. [12] introduced the glucose clamp technique to measure IR \textit{in vivo} and allowed researchers to prove that MetS and atherosclerotic vascular disease are associated with hyperinsulinaemia and IR.[13] Therefore, Reaven defined the IR syndrome – syndrome X – as the association of IR/ hyperinsulinaemia, glucose intolerance, dyslipidaemia and hypertension.[14] On the other hand, Kaplan employed the phrase “Deadly Quartet” to characterise a pattern of risk factors that included obesity, glucose intolerance, hypertriglyceridaemia and hypertension.[15]

In 1998 [16], the World Health Organization was the first organisation to provide a united definition of MetS with diabetes or impaired glucose tolerance as major clinical features and two other clinical features such as hypertension, hypertriglyceridaemia, low high-density lipoprotein cholesterol (HDL-C) levels, obesity or elevated waist/hip ratio or microalbuminuria. In 2001,[17] the National Cholesterol Education/Adult Treatment Panel (NCEP ATP) III defined MetS by ≥3 of waist circumference >102 cm in men or >88 cm in women, fasting glucose ≥110 mg/dl (6.1 mmol/l), subsequently revised to ≥100 mg/dL (5.6 mmol/l) or treatment for diabetes, BP ≥ 130 mm Hg systolic or ≥85 mm Hg diastolic or treatment for hypertension, triglycerides (TG) ≥150 mg/dl (1.7 mmol/l) or HDL-C < 50 mg/dl (1.3 mmol/l) for women or <40 mg/dl (1.0 mmol/l) for men. Over the years, the MetS has been given many names, including syndrome X, Reaven’s syndrome, IR syndrome, deadly...
quartet, DROP syndrome (dyslipidaemia, IR, obesity and high BP), dysmetabolic syndrome, syndrome X plus [18,19] and visceral adiposity syndrome.[20] However, MetS is the most commonly used name [21,22] suggested also by the International Diabetes Federation (IDF) [23] and American Heart Association; National Heart, Lung and Blood Institute (AHA/NHLBI). [21] The IDF Panel suggested the presence of abdominal obesity necessary for MetS diagnosis and two additional factors originally listed in the NCEP ATP III definition (see above) and emphasised ethnic differences in the correlation between abdominal obesity and other MetS risk factors.[23] The AHA/NHLBI panel emphasised that MetS is highly associated with the presence of abdominal obesity, shows considerable variation in the components among different individuals, increases the risk of developing both atherosclerotic CVD and type 2 diabetes mellitus and is a secondary target for reducing CV events with lifestyle interventions such as smoking cessation, lowering the levels of LDL-C and BP management. They recommended drug therapies for abnormalities in the individual risk factors if lifestyle changes are not adequate.

The prevalence of the MetS varies from 4 to 84%.[24] These differences can be attributed to the criteria used to define MetS, as well as by other parameters such as age, gender, study population and ethnic differences.[25–27] The characteristics of the MetS may be present in children and adolescents, but its prevalence increases with age. [28] Using data from the National Health and Nutrition Examination Survey III (NHANES III) and the NCEP ATP III criteria, the age-adjusted prevalence of the MetS in the United States is currently estimated at 24% and this increases to 44% in >60 years old adults.[24] Concerning gender, there are no definite conclusions since the MetS prevalence based on gender varies among studies. Athyros et al. did not find any difference between Greek men and women,[29] while Ilanne-Parikka et al. found a higher prevalence in Finnish men than women.[30] On the other hand, Ozsahin et al. as well as Lee et al. reported a higher prevalence in Turkish and Korean women, respectively. [31,32] Furthermore, high risk of MetS may be transmitted from fathers and mothers to sons and daughters.[33]

Since cigarette smoking plays a substantial role in the pathogenesis of numerous chronic diseases such as cardiovascular (CV) disease (CVD), cancer, lung disease and others, we will review the role of cigarette smoking status (active/cessation) in relation to the MetS.

**MetS and cigarette smoking status**

The National Institute of Drug Abuse describes nicotine as one of the most heavily used addictive drugs available (NIDA, 2009). Globally, >1 billion people are smokers, which is around one third of the adult world population. [34] Many studies reported a higher incidence of MetS in smokers. [35,36] Miyatake et al. reported that cigarette smoking is closely linked to MetS in the Japanese population.[37] A meta-analysis of 13 prospective cohort studies, involving 56,691 participants and 8688 MetS cases from Europe, Asia and North America found that active smokers have a 26% increased risk of MetS compared with non-smoking subjects.[38] For women, no correlation with smoking and MetS was observed. However, Slagter et al. [39] evaluated data of 24,389 men and 35,078 women who participated in the Life Lines Cohort Study and reported that active smoking is correlated with an increased risk of MetS in both genders (odds ratio 1.7–2.4 for men, 1.8–2.3 for women, all p values < 0.001), irrespective of their body mass index (BMI). This increased risk was related to lower HDL-C, higher TGs and waist circumference. Also, Hwang et al. [40] in a cross-sectional study included 1852 men >40 years old, who underwent health screening, found positive dose–response correlation with smoking levels (non-, intermediate and heavysmokers) and MetS. The CASPIAN-III Study included 5625 students, aged 10–18 years [41] and confirmed that both smoking and exposure to smoke are associated with an increased risk of MetS and some of the cardiometabolic risk factors. The authors touch on the very important issue that passive smoking should be considered as a health priority in the paediatric age. Yankey et al. conducted multiple logistic regression analyses using data from the 2011–2012 United States NHANES to estimate relationships between cardiometabolic risk factors and increasing years of smoking cigarette use. [42] They reported that increased years of cigarette use are significantly associated with increased odds of hypertension (OR = 1.03; 95% CI: 1.00, 1.06) and hyperglycaemia (OR = 1.03; 95% CI: 1.01, 1.05) after adjusting for confounders. Furthermore, Wada et al. [43] evaluated 22,892 Japanese who visited the health care centre at Jikei University Hospital in Tokyo for medical check-ups and reported that not only current smoking habits, but also past smoking may contribute to the occurrence of MetS. However, due to the existence of the so-called “smoking paradox”, the impact of this risk factor on CVD mortality is still not clear. Bundhun et al. [44] evaluated 100 studies consisting of 884,190 patients after percutaneous coronary intervention (PCI) and reported a higher long-term mortality in MetS patients and an unexpectedly, significantly lower overall mortality risk among smokers (3.37% compared with non-smokers 5.13%). The existence of a “smoking paradox” has also been observed in other studies. For example, Hasdai and Holmes found lower adverse outcomes in smokers compared to non-smokers after PCI. [45] The probable explanations could be that, study follow-ups are short, most of the non-smokers were diabetics and suffered from hypertension, while smokers were
presenting with coronary heart disease at younger age, have more favourable clinical and angiographic profile and less damage to microvascular function. In contrast, other studies reported different results. Jang et al. [46] found that individuals who continue smoking after PCI experienced worst outcomes compared with non-smokers. Also, Castela et al. [47] reported a higher rate of vascular complications, but a similar mortality rate between smokers and non-smokers at 1 year.

**Influence of cigarette smoking on MetS risk**

Smoking cigarettes may increase the risk of MetS or worsen it by several mechanisms. The main ones are described below.

**Release of nicotine**

Nicotine facilitates synaptic transmission of the neurotransmitter at the neuromuscular junction and ganglia by binding to various types of nicotinic acetylcholine receptors (nAChRs, commonly locating in the brain and peripheral nervous system).[48] This provokes the release of numerous essential neurotransmitters and hormones such as arginine vasopressin and corticotropin-releasing hormone, adrenocorticotropic hormone, growth hormone (GH), dopamine, serotonin, glutamate and γ-aminobutyric acid in the central nervous system, acetylcholine (Ach) in the central and peripheral nervous system, epinephrine and norepinephrine by the adrenal medulla, cortisol by the adrenal cortex.[49,50] Note that the hypothalamic–pituitary–adrenal axis [51] and the renin–angiotensin–aldosterone system [52] have been implicated in those processes. The release of norepinephrine, dopamine, serotonin and γ-aminobutyric acid suppress eating; elevate thermogenesis in adipose tissue [increase lipolysis and the subsequent recycling of fatty acids (FAs) into TGs]. Active smoking has a complex effect on those hormones. The acute effects of active smoking lead to decrease of appetite and increase metabolic rate, while the chronic effects of active smoking increase appetite and decrease metabolic rate.[49] In addition, nicotine also increases the likelihood of IR and excess cortisol, which may be involved in the association of smoking with abdominal obesity.[49]

**Provoke inflammatory reactions**

The inflammatory reactions found in smokers may increase the risk of MetS or worsen it. High levels of inflammatory biomarkers have been shown to be elevated in subjects with MetS.[53,54] Also, levels of C-reactive protein (CRP, classic marker of systemic inflammation) have been shown to be noticeably elevated in smokers compared with non-smokers [55–57] and may be related to the pathogenesis of type 2 diabetes.[58]

**Influence on leptin, adiponectin and ghrelin levels**

Leptin and adiponectin are secreted by adipose tissue and both belong to adipokines. Leptin has been recognised as a major endocrine marker in the homeostatic control of body weight.[59,60] Leptin is also involved in the recruitment, activation and survival of inflammatory cells.[61] Adiponectin, has been shown to possess insulin sensitising, anti-inflammatory and anti-atherogenic properties.[62,63] Both cigarette smoking and obesity are accompanied by a low-grade subclinical chronic inflammation. Despite the well-known inverse association between smoking and body weight, there have been conflicting reports on the effects of smoking on serum leptin and adiponectin levels.[64–69]

Ghrelin is a neuroendocrine hormone secreted primarily by the stomach that stimulates appetite directly via activation of the GH secretagogue receptor 1a (GHSR-1a) in the hypothalamus, and indirectly by increasing expression of orexigenic peptides, such as neuropeptide Y.[70,71] MetS is associated with lower levels of ghrelin, and progressively lower ghrelin levels are associated with increasing MetS severity, although, Leinonen et al. [72] reported that this association can be diminished after years.

**Impaired plasma lipid profile**

Both animal and human studies have found that cigarette smoking significantly increases levels of plasma total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C) and decreases HDL-C.[73–77] Exposure to cigarette smoke may lead to oxidative stress and plasma antioxidation depletion.[78] Thus, HDL particles may undergo changes in structure or composition, losing their normal biological behaviours [79] and cannot protect LDL particles against oxidation and may even act negatively in the reverse cholesterol transport pathway.[79]

Exposure to cigarette smoke may influence cortisol production.[80] Already 30 years ago, it was reported that smokers have higher fasting plasma cortisol levels compared with non-smokers.[81] This leads to accumulation of abdominal fat,[82] which, in turn, increases waist circumference, plasma TGs and decreases HDL-C. Also, another mechanism could be the increased release of free FAs due to low lipoprotein lipase activity,[83] higher 3-hydroxy-3-methylglutaryl-CoA reductase activity and higher glucose-6-phosphatase dehydrogenase activity. [84] All the above stimulate the hepatic synthesis of very low-density lipoprotein leading to increased TGs concentration in plasma. Furthermore, together with elevated
TGs and low HDL-C levels the small dense LDL (sdLDL) can be identified.\cite{85} Abdominal obesity and IR may be responsible for sdLDL particle formation; an essential mechanism is increased free FA release from adipocytes, which stimulates hepatic TG output.\cite{86} Moreover, if fatty liver is present (frequently found in MetS), \textit{de novo} synthesis of TGs is increased.\cite{87,88} Fatty liver may affect LDL particle size independently of both abdominal obesity and IR.\cite{87} Currently, there is increased interest in the usefulness of measuring non-fasting TGs,\cite{89} as a more powerful and independent predictor of CVD risk than fasting levels.\cite{90} Furthermore, an expert panel, in 2011, provided a consensus statement on the definition and classification of non-fasting TG levels.\cite{91} Average values for postprandial TG levels were recommended based on a meta-analysis.\cite{92}

**Obesity and smoking**

In the Framingham study, life expectancy of obese active smokers is shortened by 13 years compared with normal weight non-smokers and 1/3–1/2 of obese smokers died between the ages of 40–70 years compared with approximately 10% of normal weight non-smokers.\cite{93} Obesity may lead to adipose dysfunction due to systemic oxidative stress.\cite{94} One proposed mechanism by which obesity produces oxidative stress is mitochondrial and peroxisomal oxidation of FAs, which can generate reactive oxygen species in oxidation reactions. Malondialdehyde (MDA), a lipid peroxidation end product, is increased in conditions marked by obesity and IR. In the Multi-Ethnic Study of Atherosclerosis study,\cite{76} smokers had a lower prevalence of IR compared with non-smokers, probably because of lower BMI. However, when adjusted for BMI, smokers were still at higher risk of MetS. Data from NHANES III indicated that when adjusted for modifiable lifestyle factors active smoking was correlated with higher risk of MetS compared with non-smoking, when adjusted for BMI for both men and women.\cite{95} Nowadays, there is no doubt that cigarette smokers are more likely to have lower BMI,\cite{96} although they seem to have increased abdominal adiposity.\cite{97–99} Central adiposity, which reflects visceral fat deposition, seems to be a better indicator of the adverse metabolic consequences of obesity than over-all adiposity.\cite{100}

**IR**

One of the major factors linking smoking and MetS is IR. IR is able to enhance expression of pro-inflammatory cytokines, resulting in systemic stress.\cite{94} In addition to MDA, F-2 isoprostanes (F2-IsoPs) are also a product of polyunsaturated FA peroxidation.\cite{101} Studies have reported that BMI is significantly correlated with the F2-IsoP concentration.\cite{102,103} Another marker of oxidative stress is urinary 8-iso prostaglandin F2\textsubscript{α} (8-iso PGF\textsubscript{2α}) which positively correlates with obesity and IR.\cite{104}

The increased IR in smokers is provoked by the actions of cotinine (the metabolite of nicotine), carbon monoxide (CO), cortisol, the sympathetic nervous system and GH.\cite{105} Cotinine induces a low-level inflammation response \cite{81} and nicotine, CO, cortisol, the sympathetic nervous system and GH activate anti-oestrogen effects and finally reduce insulin sensitivity.\cite{106} Facchinetti et al. reported that plasma glucose levels in response to the oral glucose load were similar in non-smokers and smokers, but the plasma insulin responses of the smokers were significantly higher.\cite{107} IR was dose dependently related to smoking.\cite{108} Furthermore, in healthy men, chronic smoking was associated with high plasma insulin concentrations, independent of other factors known to influence insulin sensitivity.\cite{109}

**Smoking cessation and MetS**

Several studies have shown that individuals who quit smoking tend to increase their body weight.\cite{110} The possibility of gaining weight can stop smokers from quitting and increases the risk of relapse, particularly in women.\cite{111} However, Sherrill-Mittleman et al.\cite{112} in the study involving 35,986 young US Air Force recruits (mean age 20 years) reported that although there was a statistically significant relationship between smoking and body weight in White males, the effect range was about 1 kg. Thus, the differences in body weight between young smokers and non-smokers are marginal and it would take years to increase the differences usually seen in adult smokers. Of note, Wada et al.\cite{43} found that after smoking cessation, the OR of MetS increased and was the highest (1.36; 1.16–1.60) in the first 5 years and subjects who smoked ≥20 cigarettes before cessation had an increased risk of MetS in the next 20 years. Also, Calo et al.\cite{113} found that MetS was more prevalent in former smokers (48.4%) compared with active (42.7%) and non-smokers (40.0%). Kim et al.\cite{114} also observed this pattern (8.0% in non-smokers, 7.1% in new smokers, 17.1% in ex-smokers and 13.9% in active smokers, \(p < 0.001\)). In contrast, de Oliveira Fontes Gasperin et al.\cite{115} analysed data from 986 employees of an Austrian company obtained during their annual medical check-up at their workplace. No differences in total body fat and/or body fat distribution were found between non-smokers, active smokers and ex-smokers; conversely, in regular smokers, the number of cigarettes smoked per day was significantly associated with higher body weight and BMI. Contrary to the beliefs of many smokers, heavy smoking is associated with higher body weight and unfavourable metabolic changes. Data from 21,828 individuals (population-based cohort study)
showed that current smokers had higher waist to hip ratio than non-smokers, which is modified after smoking cessation. This can be explained by several mechanisms such as increased energy intake, decreased resting metabolic rate, decreased physical activity and increased lipoprotein lipase activity. Furthermore, smoking cessation is associated with increased plasma adiponectin levels. Early abstinence from cigarette smoking seems to be associated with increased plasma concentration of ghrelin. This could be one reason for increased food craving during nicotine withdrawal and subsequent weight gain. Additionally, weight loss associated with smoking may be caused by a reduction in lean mass rather than fat mass, which may not be fully differentiated by the BMI. The biological mechanism explaining the association of smoking and abdominal fat distribution is not well explained. One explanation could be that smoking may have an anti-oestrogenic effect by increasing the 2-hydroxylation of oestradiol or disturbing the androgenic/oestrogenic balance. Cigarette smoking may also stimulate the activity of lipoprotein lipase of adipose tissue resulting in increased uptake and storage of TGs which ends with increased fat mass. Nevertheless, increased abdominal fat in smokers may only reveal underlying differences in the lifestyle patterns between smokers and non-smokers, such as alcohol and caloric intake, physical activity or educational level.

Conclusions

Changing lifestyle could drastically reduce the prevalence of MetS parameters. Thus, tobacco control policies, such as preventing smoking initiation and evidence-based cessation programmes, are necessary to reduce the burden of MetS. The major problem is not the lack of efficacy of available therapeutic measures, medication and treatments, but their inadequate application. Family history is essential; care should be focused to children at risk (from families presenting MetS, diabetes mellitus, obesity, cigarette smoking use and others). Thus, early detection of MetS factors is likely to lower not only its incidence in childhood, but it could also considerably lower the prevalence of MetS in the adult population.

Disclosure statement

No potential conflict of interest was reported by the authors.

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