Relationship between smoking and metabolic syndrome

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Obesity and smoking are important causes of morbidity and mortality worldwide. The diseases and conditions associated with smoking make tobacco use one of the leading causes of death worldwide. In the World Health Organization European region, overweight and obesity are responsible for many chronic diseases, causing more than one million deaths each year. Smoking cessation is associated with a significantly reduced mortality risk in every body-mass-index group. Reductions in smoking and obesity would increase both the psychophysical well-being of the population and its economic productivity; it would also reduce the direct costs of pharmacological therapies and other forms of treatment. The aim of this review is to critically evaluate how tobacco smoking and obesity interact to reduce life expectancy, and to offer a comprehensive view of this issue that should be useful for clinical practice.

INTRODUCTION

Obesity, with its comorbidities, and smoking are important causes of morbidity and mortality worldwide.[1,2] The diseases and conditions associated with smoking make tobacco use one of the leading causes of death in the world,[3] accounting for about five million deaths annually, which is equivalent to 1 in 10 adults globally.

According to the Framingham study, obese individuals who smoke have a 14-year reduction in life expectancy at the age of 40 years.[4] A large prospective study showed that smoking coupled with obesity contributes substantially to all-cause mortality, with a 3.5–5-fold greater risk for severely obese current smokers than for normal-weight nonsmokers.[5]

It is clear that smoking and obesity are the main causes of preventable morbidity and mortality in developed countries.[6] In the context of the current worldwide obesity epidemic, and with the high prevalence of smoking, it is very important to understand the relationship between smoking and obesity.

The aim of this review is to offer a comprehensive view of the interaction between tobacco smoking and obesity and to underline how this interaction, far from being an efficient way to control body weight, leads to a global reduction in life expectancy.

DEFINITION OF METABOLIC SYNDROME

The metabolic syndrome (MBS) is a disease of adulthood, recently classified nosologically and subject to etiopathogenetic and epidemiological redefinitions.[7] Currently, MBS is a widely accepted concept applied to centrally obese patients with an increased risk of cardiovascular disease and diabetes.[8] From a physiopathological perspective, this syndrome is associated with multiple metabolic changes and hemodynamic disorders, such as reduced glucose tolerance, type 2 diabetes, insulin resistance, arterial hypertension, altered lipid metabolism (hypertriglyceridemia, hypercholesterolemia, reduced high-density lipoprotein, and elevated low-density lipoprotein), and abnormalities of the coagulation system. In these patients, there is a very high risk of complications, especially vascular ones, such as atherosclerotic disease, acute myocardial infarction, and stroke.[9,10]

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Although the clinical importance of this syndrome is recognized today, many uncertainties remain and a lively debate on its diagnostic criteria is ongoing. Although MBS was identified 40 years ago, the actual criteria that define this syndrome have been formulated very recently. There are currently five definitions of MBS, issued by five different scientific associations: the World Health Organization (WHO),[11] the National Cholesterol Education Program–Adult Treatment Panel III (NCEP–ATP III),[12] the American Association of Clinical Endocrinologists,[13] the European Group for the Study of Insulin Resistance,[14] and the International Diabetes Federation.[15]

It is important to emphasize that when any definition is considered, each diagnostic criterion is in itself an independent risk factor for cardiovascular events, and increases the risk of such events by 30%.[16]

There is a high prevalence of MBS in the general population, varying from 17.8% to 34.1%, depending on whether the WHO or NCEP-ATPIII diagnostic criteria are used, respectively. The maximum peak age is between 65 and 74 years.[17] With the increased incidence of obesity in young populations, these data may well change over the next few years. We should bear in mind that all ethnic groups are affected and that the risk of cardiovascular events is almost double the risk in unaffected subjects. A study published by the *Journal of the American Medical Association* in 2002[18] reported a prevalence of MBS of greater than 40% in the US population. In Europe, low-prevalence areas (17% in men and 8% in women in Finland) contrast sharply with regions where its prevalence is high, such as the Mediterranean.[19] In Italy, for example, MBS affects 23% of men and 21% of women. The prevalence of MBS among menopausal women is particularly significant, reaching up to 32%.[17] It is also important to note that 5% of adolescents are affected by MBS.[20]

ASSOCIATION BETWEEN TOBACCO SMOKING AND METABOLIC SYNDROME

Smoking is widely accepted as a major risk factor for cardiovascular disease.[21] Previous studies have shown that smoking reduces insulin sensitivity, induces insulin resistance,[21–26] and enhances cardiovascular risk factors, such as elevated plasma triglycerides,[27–30] reduced high-density lipoprotein–cholesterol,[27–31] and hyperglycemia.[22] Several studies have also shown that smoking is associated with metabolic abnormalities and increases the risk of MBS.[32–34]

Nakanishi et al.[32] reported that subjects who habitually smoked tobacco had a 1.07–1.66-fold greater risk of developing MBS than subjects who did not smoke. Weitzman et al.[20] have demonstrated for the first time a dose-responsive, cotinine-confirmed relationship between tobacco smoke and the severity of MBS. Weitzman's study also demonstrated an association between tobacco smoke and MBS in adolescents. The authors reported that exposure to tobacco smoke, whether through active or passive smoking, is associated with a fourfold increase in the risk of the MBS among adolescents who are overweight or at risk of overweight.

Saarni et al.[35] investigated the association between adolescent smoking and overweight or abdominal obesity in adulthood. They reported that smoking is a risk factor for abdominal obesity in both sexes and for overweight in women.

In Kawada's 1-year follow-up study,[36] current smokers had a higher risk of MBS than nonsmokers, independent of age, body mass index (BMI), insulin resistance, uric acid, and other lifestyle factors. In contrast, ex-smokers did not have a significantly greater risk of MBS than nonsmokers.

The most effective way for smokers to reduce their risk of MBS and cardiovascular disease is to stop smoking.[37] However, Nakanishi et al.[32] highlighted that smoking cessation is also associated with a 1.3-fold risk of MBS as a result of subsequent body weight gain.

INSULIN RESISTANCE

The main clinical component of MBS is insulin resistance. MBS and glucose intolerance are regarded as disturbances with a common background and strong interrelationship.[38] Cigarette smoking may directly reduce insulin sensitivity by increasing circulating levels of insulin-antagonistic hormones (i.e., catecholamines, cortisol, and growth hormone) and increasing lipolysis, resulting in high circulating levels of free fatty acids.[32] Nicotine, carbon monoxide, and other metabolites derived from smoking also play important roles in insulin resistance. Furthermore, several mechanisms by which cigarette smoking promotes dyslipidemia have been proposed, including reduced lipoprotein lipase activity, increased 3-hydroxy-3-methylglutaryl-CoA reductase activity, increased glucose-6-phosphatase dehydrogenase activity, and increased central obesity.[27] Other studies may have lent some insight into this process, in that recent work has indicated that epigenetic mechanisms may be involved in MBS and type 2 diabetes.[39–41]

There is important evidence that variation in DNA methylation patterns is linked to various pathological conditions, including insulin resistance,[39] and that it may be responsible for MBS onset, beginning from developmental programming in the prenatal period.[39] It has been demonstrated[42] that smoking is related to aberrant DNA methylation patterns and that one of the mechanisms by which tobacco smoke promotes lung cancer is the inactivation of key genes through pro-

moter hypermethylation.[43] The literature suggests that a plausible underlying biological mechanism is required to explain the impact of tobacco smoke on MBS pathogenesis.

The insulin response to oral glucose loading is more pronounced in smokers than in nonsmokers,[22] and insulin resistance is dose-dependently related to smoking.[44] In healthy men, chronic smoking is associated with high plasma insulin concentrations, regardless of other factors known to influence insulin sensitivity.[45] The long-term use of nicotine gum is also associated with hyperinsulinemia and insulin resistance.[46] In nonobese men, insulin sensitivity improved 8 weeks after smoking cessation, despite a body weight increase.[47] The risk of type 2 diabetes is also greater in smokers than in nonsmokers.[48,49]

In the Physicians' Health Study, a 70% greater risk of diabetes was reported in men who smoked more than 20 cigarettes a day than in nonsmokers.[50] Similar observations were made for women.[51–53] The risk of diabetes in former smokers decreases progressively as the length of time since smoking cessation increases,[53,54] and it returns to normal after a few years.[53] Smoking appears to aggravate insulin resistance in individuals with type 2 diabetes[55] and impairs glycemic control.[48]

Overall, despite some conflicting observations, the evidence indicates that smoking leads to visceral fat accumulation and insulin resistance, and it increases the risk of MBS and type 2 diabetes.

CENTRAL OBESITY

Insulin resistance is the primary consequence of localized visceral fat. There are two mechanisms responsible for a reduction in insulin sensitivity in the peripheral tissues[56]: 1) excessive accumulation of fat, with the development of an inflammatory state, increased production of proinflammatory cytokines[57] by adipocytes, and infiltration of macrophages into the adipose tissue; 2) metabolic variations in the same adipocytes, which reduce their capacity to store fats that consequently migrate to other nonadipose organs, such as the liver, heart, muscle, and pancreas, causing a toxic response known as "lipotoxicity."[58]

Mizuno et al.[59] reported that waist circumference is significantly higher in obese subjects who smoke than in those who do not. Smoking seems to accelerate visceral fat accumulation and promote obesity-related disorders. Waist circumference is strongly associated with visceral fat mass,[60] which is influenced by the plasma cortisol concentration.[61] Smokers have higher fasting plasma cortisol concentrations than nonsmokers.[62,63] Higher cortisol concentrations may be a consequence of the stimulation of sympathetic nervous system activity, which is induced by smoking.[64,65]

Sex hormones may also be involved.[66] Women's visceral fat mass increases when their estrogen concentrations decrease and their testosterone concentrations increase, typically after menopause.[66] In other situations, lack of estrogens and excess androgens have been associated with visceral adipose tissue accumulation in women,[67,68] as is also reported after the administration of testosterone.[69] Female smokers show no change in their absolute estrogen concentrations, but they have higher androgen concentrations[63,70] and lower bioavailable estrogens[71] than do female nonsmokers. Testosterone concentrations may also be affected by smoking, although the data are inconsistent.[72,73]

In men, visceral fat increases when testosterone concentrations decrease,[74] and the administration of testosterone to middle-aged men reduces their visceral adipose tissue by increasing lipolysis.[75] Smoking may reduce testosterone concentrations in men.[76] Overall, these results suggest that, in addition to excess cortisol, an imbalance between male and female sex hormones in women and a reduction of testosterone in men may be involved in the effect of smoking on visceral adipose tissue.

TOBACCO USE AND OREXIGENIC HORMONES

Leptin has received attention for its possible association with body weight and tobacco use. The presence of insulin resistance in long-term nicotine gum chewers[77] suggests that nicotine is the major constituent of tobacco responsible for these metabolic aberrations. Leptin levels are higher in women,[78,79] and they are directly related to a larger fat mass.[80] It has recently been speculated that leptin also has metabolic effects and that resistance to the effects of leptin constitutes a link between obesity and insulin resistance.[81]

Leptin is a peptide hormone released by adipose tissue that signals the extent of fat storage. It binds to hypothalamic receptors, modulating the release of neuropeptides with anorexigenic and orexigenic effects.[82,83] Individuals with similar adiposity patterns show remarkable differences in their serum leptin levels,[84] indicating that this sequence of events is neither linear nor similar in all individuals. The relationship between leptin and adiposity is even more complex if more than one factor, such as tobacco use, is involved.

Smokers should be expected to eat less and show higher energy expenditure because of the high levels of circulating leptin induced by inhaled nicotine. It would be reasonable to infer that high serum levels of leptin are responsible for the lower BMIs seen in smokers, because leptin, when bound to its hypothalamic receptors, promotes the release of anorexigenic neurotransmitters, leading to a reduction in body weight.[82] The chronic use

of tobacco may elevate serum levels of leptin, increasing the expression of leptin or reducing its renal depuration. Also, leptinemia may be influenced by nicotine through induction of corticosteroid release.[83]

Many studies[77,82,83] have generated results that support the hypothesis that the higher levels of leptin in smokers originate from a resistance mechanism that leads to lower hormone sensitivity. However, there are conflicting results in the literature about the serum levels of leptin in smokers.[83–85] Some studies[86,87] have found that leptin levels are significantly lower in smokers than in nonsmokers after adjustments are made for BMI, sex, and age. Other studies[88,89] suggest that leptin levels are not associated with smoking. Several investigations have shown, however, that long-term use of nicotine is associated with elevated circulating leptin levels. These results support the view that leptin is directly or indirectly related to insulin sensitivity in men.

Leptin levels have also been evaluated after smoking cessation, with equally contradictory findings. A significant increase in postcessation serum leptin levels, rather than the expected reduction, has been demonstrated in some studies.[83,90] It is important to emphasize that the discrepancies among studies can be explained by differences in such factors as ethnic groups, age, and health status of the participants.[90] Another possible explanation is that nicotine could indirectly modify leptin levels, thereby maintaining a low BMI and increasing leptin sensitivity.[90]

Conflicting findings regarding the relationship between leptinemia and smoking status can also be explained by a difference in the hormone receptors. Genetic variations in the leptin receptor have been correlated to overweight and obesity,[91–94] while an association with smoking cessation has not yet been confirmed. Martin et al.[84] reported that the effects of smoking are linked to certain specific genotypes and circulating leptin, suggesting that genetic inheritance could partly explain different leptin concentrations in smokers, nonsmokers, and individuals in course of cessation. Leptin levels may be affected by sex, menopause, phase of the hormonal cycle, and by central or peripheral fat deposit.[95]

Discrepancies have also been reported regarding the levels of other peptides that regulate food intake, such as neuropeptide Y,[96] orexins,[97] and ghrelin.[90] The administration of inhaled nicotine markedly reduced the food intake of rats by inhibiting the synthesis of neuropeptide Y, one of the orexigenic hormones.[98,99] Therefore, smokers may eat less because of increased leptin activity (or leptin receptors activity) with subsequent reduced liberation of neuropeptide Y. During smoking cessation, the lack of nicotine may reduce leptinemia, thus decreasing leptin inhibitory effects on neuropeptide Y, and, finally, increase appetite.[100] Ghrelin is another hormone involved in the regulation of satiety and hunger. It induces appetite in an action mediated by neuropeptide Y. Some studies reported that serum levels of ghrelin are associated with smoking status, but not to the number of cigarettes consumed per day.[101]

Contrary to expectations, Lee et al.[90] reported that after smoking cessation, the concentration of leptin in serum increases, whereas that of ghrelin decreases. These findings demonstrate that the changes in the leptin–ghrelin–neuropeptide Y system might be the consequence, rather than the cause, of the changes in body weight observed after smoking cessation, probably correlated with the lack of nicotine's direct effects on the central nervous system.[90]

SMOKING CESSATION AND WEIGHT GAIN

Cigarette smoking is a leading preventable cause of death and disability, but weight gain after quitting smoking[64,85,102] is commonly cited as a primary reason for not trying to quit or for relapsing after cessation. Women seem to be somewhat more susceptible to weight gain following smoking cessation than men. In a 10-year study, the mean weight gain attributable to smoking cessation was 5.0 kg in women and 4.4 kg in men.[103] Multiple studies have shown that 33–75% of ex-smokers report weight gain within the first year of cessation.[104]

Numerous cross-sectional studies have indicated that BMI is lower in cigarette smokers than in nonsmokers,[101,102,105] and that leanness correlates directly with the duration but not the intensity of smoking. Generally, the literature reports an association between a longer duration of smoking and a lower BMI.[103,106,107]

Recent statistical analyses of datasets from both the 2005–2006 National Health and Nutrition Examination Survey[105] and the 2005 National Health Interview Survey[108] confirm the findings of previous studies that smokers weigh significantly less than nonsmokers. However, Kim et al.[109] reported that continuous smokers show a greater weight gain than nonsmokers and they speculated that continuous smokers are less physically active. Another recent study[110] reported no significant differences in the mean BMIs of smokers and nonsmokers among either males or females.

The exact cause of weight gain after smoking cessation is unclear. Two main hypotheses are reported in the literature. The first is that smoking increases energy expenditure because nicotine increases the metabolic rate, so energy expenditure is reduced with cessation.[104,111,112] In 1986, Hofstetter et al.[113] reported that the 24 h energy expenditure by smokers is increased by 140–200 kcal/day on a day with smoking relative to that

on a day without smoking, with no corresponding change in the mean basal metabolic rate. Further studies have since yielded conflicting results, predominantly finding an increase in the resting metabolic rate (RMR) shortly after nicotine administration. Walker et al.[114] found a 6% increase in RMR after 20 min of smoking and Dallosso et al.[112] reported a 3% increase in RMR after smoking a single cigarette. However, several studies have failed to find a corresponding increase in RMR, when measured before and after smoking a single cigarette.[115,116] Bradley et al.[110] measured energy expenditure with doubly labeled water in a group of current smokers during a 2-week period in which the subjects lived at home and undertook their normal activities, and reported that the total energy expenditure of the male and female smokers did not differ significantly from that of nonsmokers. Although the total number of current smokers was small (only 47 individuals), the evidence reported in that study indicates that weight gain following smoking cessation is the result of increased caloric consumption and reduced total energy expenditure. The second hypothesis explaining the weight gain observed after tobacco cessation is that smoking alters energy intake by inducing an anorexic effect,[111] and by extension, smoking cessation leads to weight gain because of increased appetite and intake.[117]

CONCLUSION

An important consequence of smoking is a hormonal imbalance that is conducive first to an accumulation of central fat, and then to insulin resistance. The latter condition may represent a major link between cigarette smoking and the risk of cardiovascular disease.[37]

Current smokers have the highest mortality rates across all BMI and waist circumference groups,[118] and smoking cessation is associated with a significantly lower mortality risk in every BMI and waist circumference group. The longer someone is a former smoker, the lower their mortality risk.[119] Although losing weight may reduce the mortality risk in current smokers, smoking cessation is related to a stronger reduction in risk.

It is well known that smoking cessation is associated with weight gain[64] and an increase in waist circumference,[120] possibly because of a reduced metabolic rate and increased caloric intake.[117] However, weight gain is not likely to counteract the health benefits of smoking cessation. A recent study based on data from the National Health and Nutrition Examination Survey showed that a substantial reduction in smoking prevalence has only a small effect on increasing the prevalence of obesity and reducing the prevalence of healthy weight.[102] Moreover, smoking cessation has the great benefit of reducing the risk of MBS, especially in subjects with fatty liver.[121]

These findings indicate that greater emphasis should be placed on the risk of central obesity, insulin resistance, and associated conditions among smokers, in particular, although concerns about post-cessation weight gain may deter many individuals from quitting smoking. Smokers should be made aware that smoking is not an efficient way to control body weight, does not help prevent obesity, and could favor visceral fat accumulation and increase the risk of MBS and diabetes. It is, indeed, clear that visceral obesity is a factor that should itself be considered a type of pathology, and which must be tackled as early as possible.

This is a perspective of great interest to all parties involved in primary and secondary prevention. To emphasize the importance of an early approach to this problem, it is important to remember the extent of the obesity problem. It is estimated that in the WHO European region, overweight and obesity are responsible for approximately 80% of type 2 diabetes, 35% of ischemic heart disease, and 55% of hypertension cases in adults, causing more than one million deaths each year and 12 million life-years spent in poor health.[122]

It is also estimated that obesity is responsible for approximately 6% of national healthcare assistance costs.[123] Therefore, a reduction in smoking and smoking-related obesity will increase the psychophysical well-being of the population and its economic productivity. This would be accompanied by a reduction in pharmacological therapies and other forms of treatment, resulting in a considerable reduction in direct costs.

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