

Review Article

Smoking and changes in body weight: Can physiopathology and genetics explain this association?*

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Abstract

Tobacco use is the leading preventable cause of death in most countries, including Brazil. Smoking cessation is an important strategy for reducing the morbidity and mortality associated with tobacco-related diseases. An inverse relationship between nicotine use and body weight has been reported, in which body weight tends to be lower among smokers than among nonsmokers. Smoking abstinence results in an increase in body weight for both males and females. On average, sustained quitters gain from 5 to 6 kg, although approximately 10% gain more than 10 kg. Pharmacological treatment for smoking cessation attenuates weight gain. The importance of smoking cessation as a contributing cause of the current obesity epidemic has been little studied. In the USA, the rate of obesity attributable to smoking cessation has been estimated at approximately 6.0 and 3.2% for males and females, respectively. Although the mechanisms are unclear, there is evidence that dopamine and serotonin are appetite suppressants. The administration of nicotine, regardless of the delivery system, acutely raises the levels of these neurotransmitters in the brain, reducing the need for energy intake and consequently suppressing appetite. In addition, nicotine has a direct effect on adipose tissue metabolism, influencing the rate of weight gain following smoking cessation. Leptin, ghrelin and neuropeptide Y are substances that might constitute factors involved in the inverse relationship between nicotine and body mass index, although their roles as determinants or consequences of this relationship have yet to be determined.

Keywords: Smoking; Body weight changes; Nicotine; Body mass index; Leptin; Peptide hormones/ghrelin.

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Submitted: 10 May 2007. Accepted, after review: 13 August 2007.

Introduction

Tobacco use is a serious public health problem in most countries. It is associated with approximately 400,000 deaths annually, and approximately one-third of the adult population smokes.⁽¹⁾ In various countries, this number has been decreasing. In 2002, approximately 23% of the adult population in the USA smoked. This prevalence was similar to that in Brazil.^(1,2) More recent data indicate that, in the two countries, the percentage of smokers decreased to 18.4 and 16.2%, respectively.⁽³⁻⁵⁾ The percentage of smokers is increasing even more rapidly in low-income populations of individuals with little education, a phenomenon that is repeated in less developed countries when compared to those that are more developed. It is estimated that approximately 70% of smokers will be living in underdeveloped countries in the next 20 years, inverting the present situation, in which most smokers are found in first world countries.⁽⁶⁾

Campaigns designed to educate the public regarding the hazardous effects of smoking have been widely used as a means of fighting this addiction or dependence. Other measures, such as regulating advertisements, policing the black market, increasing fees and taxes on cigarettes, as well as the restrictions on smoking in public places, have contributed to the improvements (although still incipient) in smoking control in various countries.

However, these measures will have effects on public health only over the long term. For a short-term impact, the most efficacious method is smoking cessation. However, this is not an easy target, especially in countries such as Brazil, which has scarce resources for public health.⁽⁷⁾ Although most nicotine-dependent individuals report wanting to quit smoking, fewer than 15% succeed in the long term.⁽⁸⁾

Weight gain due to smoking cessation is reported to be one of the difficulties for maintaining abstinence, especially in females. In addition, weight gain can reduce the benefits in the pulmonary functional parameters.⁽⁹⁾ Furthermore, fat deposits tend to be centrally accumulated, which is a well-known risk factor for cardiovascular diseases, diabetes and mortality in general

We intend to evaluate the present state of this issue and its repercussions in health in this text.

Smoking and body weight

The inter-relationship between smoking and body weight has been well established in various well-designed studies, most of which were published in the 1990s.^(10,11)

The body mass index (BMI) of smokers is frequently present lower than that of age- and gender-matched nonsmokers. In addition, comprehensive cross-sectional epidemiological studies, some of which considered to be classical on this subject, showed a significant inverse relationship between the regular tobacco use and body weight, which tends to be lower among smokers than among nonsmokers.^(12,13)

Smoking cessation results in weight gain both in males and females, and over 75% of smokers gain weight when they become abstinent.^(14,15)

Mean weight gain attributable to smoking cessation is 2.8 and 3.8 kg in males and females, respectively. In a systematic review of the literature, it was estimated that the mean body weight gain in individuals who quit smoking can reach 5-6 kg, and 13% of ex-smokers can gain more than 10 kg.⁽¹⁰⁾

Although most reports on smoking cessation have indicated mid- and long-term weight gain, other studies have shown that the most critical period is immediately after smoking cessation.⁽¹⁰⁾

In one study,⁽¹⁶⁾ the increase in body weight was 5.2 and 4.9 kg in females and males, respectively, during the first year after cessation, with an increase of 3.4 and 2.6 kg, respectively, in the following years. In the same study, approximately one-third of the ex-smokers gained more than 10 kg after five years of follow-up, although a more recent review of the data revealed that the mean increase might have been higher, on the order of 9.7 kg in five years, among 5887 smokers.⁽¹⁷⁾

It has been demonstrated that the risk for weight gain is highest during the first two years after smoking cessation.⁽¹⁰⁾ However, in another study, involving premenopausal females,⁽¹⁵⁾ it was shown that there is a significant difference in BMI within one week of abstinence.

The main risk factors for greater weight gain are as follows: being female; being of Afro-American descent; being below 55 years of age; consuming more than 20 cigarettes per day; and presenting low socioeconomic status.⁽¹⁸⁾

It is possible that this problem (BMI increase after smoking cessation) has repercussions other than the individual aspects. The eventual impact of this issue on public health has started to be interpreted as a contributing cause of the obesity epidemic in some countries.^(16,19) In the USA, the rate of obesity attributable to smoking cessation has been estimated at approximately 6 and 3% for males and females, respectively.⁽²⁰⁾

Whereas a few studies show that weight gain after smoking cessation might be a risk factor for relapse,^(21,22) others go even further, indicating that significant weight gain after smoking cessation is a predictive factor for lower abstinence rates.⁽²³⁻²⁵⁾

However, most of the data correlating smoking abstinence and weight gain can be called into question regarding the study methodology, since few studies were specifically designed to evaluate this possible association. Consequently, most studies show methodological biases; the lack of biochemical validation of the smoking status (by means of the determination of cotinine in serum or carbon monoxide in exhaled air); weight and height measures only reported by the patients, which are not always reliable; short follow-up periods; determination of the prevalence of abstinence rates only at a specific point in time rather than on a continuous basis; and cross-sectional (rather than cohort) designs.⁽¹⁷⁾

In addition, such studies were conducted using selected populations, such as only female patients,⁽²⁶⁾ smokers participating in smoking cessation programs,^(21,27) specific groups in society, such as the military,⁽²⁸⁾ as well as disregarding regional or national variations,⁽²⁹⁾ among other situations.

Mechanisms of weight gain during smoking cessation

The search for understanding the mechanisms that determine the relationship between the increase in BMI and smoking cessation has been intense in the past years. With this understanding, we will be able to try to control this type of weight gain so that this ceases to be a risk factor for relapse, and that overweight status, or even obesity, will not increase the risk for chronic diseases in ex-smokers.⁽³⁰⁾

The effect of tobacco use on body weight seems to be mediated by nicotine. Experimental studies using animals have indicated that the administra-

tion of this substance induces body weight loss, probably because of appetite suppression.⁽³¹⁾ In humans, tobacco use increases the adrenergic activity, which induces thermogenesis, and consequently, body weight loss. Patients using nicotine replacement therapy during the smoking cessation process present a delay in weight gain. When the medication is suspended, patients start gaining weight again.^(30,32,33)

Inhaled nicotine from cigarette smoke promotes the acute elevation of the concentration of some neurotransmitters in the brain, such as dopamine and serotonin, which are substances that inhibit food ingestion.⁽¹⁴⁾ Therefore, probably due to this mechanism, the appetite of smokers is reduced.

Despite the fact that the details of the abovementioned mechanisms are still unclear, most studies have shown that smoking cessation seems to result in weight gain, mainly because of the increase in calorie intake, although weight gain can occur with no increase in calorie intake.⁽¹⁸⁾ During smoking cessation, there is a decrease in the baseline metabolic rate, ranging from 4 to 16%, which represents less than 40% of body weight gain.⁽¹⁸⁾

In one study,⁽³⁴⁾ it was reported that energy expenditure attributable to inhaled nicotine during mild physical activity was greater than the double of that at rest: 0.51 and 0.23 kJ/kg/h, respectively. Consequently, weight gain during smoking cessation can be different among smokers with similar nicotine intake if a greater cigarette consumption occurred at rest or during daily activities.

Another aspect to be considered is the direct effect of nicotine on fat tissue metabolism, causing a higher oxidation of lipids, which helps explain the fact that BMI is lower in smokers than in nonsmokers.^(18,35)

During cessation, patients prefer to ingest foods rich in fat and sugars.⁽³⁶⁾ In addition to the increase in lipid intake during this process, other mechanisms, such as the changes in lipoprotein lipase, have been studied but remain unconfirmed.⁽¹⁸⁾

More recently, the rewarding effect or the gratification of certain types of food in smokers and nonsmokers has been investigated. In recent ex-smokers, neurochemical changes have been detected, possibly in the dopaminergic route, related to specific genetic polymorphisms. The genotypes

showing this altered behavior which have been most frequently studied are DRD2-A1 and SLC6-A3.^(37,38)

The dichotomous variable appetite/satiety is regulated by brain centers, which, in turn, are regulated by various intrinsic factors. As previously mentioned, some of these factors interact with others. For example, nicotine interacts with serotonin and dopamine. For other factors, such as leptin, ghrelin, neuropeptides with anorexigenic or orexigenic effects, and particularly among these, neuropeptide Y (NPY), this relationship has just begun to be studied.

Leptin, ghrelin, neuropeptide Y and their relationships with tobacco use

Leptin has been drawing interest as having a possible connection with the dichotomous variable appetite/satiety, body weight and tobacco use. Leptin is a peptide hormone released by fatty tissues that signalizes the size of fat storage and the nutritional state of the organism to the brain. Leptin, also called satiety hormone, bonds with hypothalamic receptors, modulating the release of neuropeptides with anorexigenic and orexigenic effects.^(39,40) This signaling is detected by the central nervous system, which, by means of the release of specific neurotransmitters, leads to, depending on the situation, the attenuation of or the increase in food intake, which is associated with, respectively, increased or decreased metabolic activity. This chain of events results in the decrease or increase in weight, in which the body weight tends to be balanced.

However, individuals with similar adiposity patterns can show remarkable differences in serum levels of leptin,⁽⁴¹⁾ indicating that this sequence of events can be neither so linear nor so similar in all individuals. This fact is more difficult to explain if more than one factor, such as tobacco use, is involved.

Following the same line of thinking, smokers would be expected to eat less and show higher energy expenditure due to the high levels of circulating leptin, induced by inhaled nicotine. It would be reasonable to speculate that high serum levels of leptin are responsible for the lower BMI seen in smokers, since leptin, when bonding with its hypothalamic receptors, would promote the release of anorexigenic neurotransmitters, leading to a decrease in body weight.⁽³⁹⁾

The chronic use of tobacco could increase the serum levels of leptin by two main mechanisms: its higher production or the decrease of its renal depuration. In addition, nicotine could induce the release of corticoids from the adrenal glands, influencing, in turn, leptinemia, in a complicated self-regulation system.⁽⁴⁰⁾ Another explanation for higher levels of leptin in smokers could be the decreased hypothalamic sensitivity to the hormone, as a resistance mechanism, leading to a rupture in the self-regulation system.⁽³⁹⁾ Various reports corroborate this possibility.^(39,40,42)

However, there are discrepancies in the literature regarding serum levels of leptin in smokers.^(18,40) In some studies,^(43,44) leptin levels have been shown to be significantly lower in smokers than in nonsmokers after adjusting for BMI, gender and age, which is a completely different finding than that expected. The divergence between results has also been reported in some studies,^(45,46) suggesting that leptin levels are not associated with smoking.

When leptin levels are evaluated after smoking cessation, the results are equally contradictory. Some studies have demonstrated a significant increase, rather than the expected decrease, in post-cessation serum levels of leptin.^(40,47) Neither could the inverse relationship between leptin levels and gradation of appetite after smoking cessation be demonstrated.⁽¹⁴⁾

It is possible that biases in the various studies, such as in the design of the investigation project, which disregarded the possible role of different ethnicities, age brackets and health status of participants, among others, can explain these discrepancies.⁽⁴⁷⁾ Neither has the potential relationship between serum levels of leptin and the dose of inhaled nicotine been considered, that is, no correction was made regarding the number of cigarettes consumed per day and the number of deep inhalations per cigarette (puffs).

In one study,⁽⁴⁷⁾ when trying to explain the findings of high leptin and low ghrelin levels two months after smoking cessation, the authors speculated that those findings were not the cause, but the result of the increase in fat mass caused by smoking abstinence.

Another possible explanation could be that smoking increased the sensitivity to leptin, and in a feedback system, it controlled fat deposition, causing a decrease in the levels of leptin. Therefore,

nicotine could indirectly modify the levels of leptin and maintain a low BMI.

It is even possible that the conflicting results between serum levels of leptin and smoking status might be explained by a different response of the hormone receptors, that is, genetic polymorphisms could determine changes in the functioning of leptin receptors. Genetic variations in the leptin receptor have been related to overweight status or even obesity,⁽⁴⁸⁻⁵¹⁾ although they have not as yet been linked to smoking cessation.

In one study,⁽⁴¹⁾ the authors found that smoking was related to certain specific genotypes and circulating leptin, suggesting that the genetic inheritance could explain, at least in part, the differences in the levels of leptin in smokers, nonsmokers and patients in the process of cessation.

It is difficult to reach a conclusion because of other very common factors that interfere with the levels of leptin, such as gender, menopause, phase of hormonal cycle and the type of fat deposit (central or peripheral). These factors should be taken into consideration in the design of future studies.⁽⁵²⁾

Conflicting findings have been reported, not only regarding the relationship between smoking and serum levels of leptin but also regarding the levels of other peptides that regulate food intake, such as NPY,⁽⁵³⁾ orexins⁽⁵⁴⁾ and ghrelin.⁽⁴⁷⁾

The parenteral administration of nicotine, as well as the administration of inhaled nicotine, has been shown to markedly reduce food intake in rats by inhibiting the synthesis of NPY, one of the hormones that increase appetite.^(31,55) In addition, there might be a direct inter-relation between leptin and NPY: when the level of one increases, that of the other tends to decrease, in a feedback loop.

Smokers, therefore, would ingest less food due to an increased activity of leptin (or of leptin receptors), with subsequent capture of this hormone in the hypothalamus, in parallel with the decrease in NPY liberation, causing a sensation of satiety. However, the lack of nicotine during smoking cessation would decrease leptinemia, and consequently, a decrease in the inhibiting effects of leptin on NPY. This would result in an increase in the production of this neuropeptide, and consequently, in appetite.⁽⁵⁶⁾

Ghrelin, a peptide produced in the stomach, is another agent involved in the satiety-hunger phenomena, since it induces appetite, in an action believed to be mediated by NPY. Some studies have

suggested that serum levels of ghrelin are related to the smoking status of patients, but not to the number of cigarettes consumed per day.⁽⁵⁷⁾

More recently, it has been demonstrated that, after smoking cessation, the serum concentration of leptin increases, whereas that of ghrelin decreases.⁽⁴⁷⁾ These results, which are contrary to what would be expected, induce further speculation: changes in the leptin-ghrelin-NPY system produced in peripheral tissues might be the consequence, and not the cause, of the changes in body weight after smoking cessation, possibly related to the direct effects of the lack of nicotine in the central nervous system.⁽⁴⁷⁾

The role of genetic polymorphisms

In addition to the abovementioned mechanisms, there are unequivocal indications that genetic variations also play a role in this bundle of phenomena. Mutations in a single nucleotide of the gene that regulates leptin production (resulting in a truncated protein) or in the leptin receptor gene (resulting in premature termination of the intracellular domain) have been shown to be responsible for morbid obesity in rats, as well as in some obesity cases in humans,⁽⁵⁶⁾ although obesity is not a monogenetic disorder.⁽⁵⁸⁾

Leptin levels increase when fatty mass increases, suggesting that obesity is a state of resistance to leptin in humans. Therefore, it has been suggested that the genetic variation of the leptin receptor locus or postreceptor defects plays a significant role in the physiopathology of human obesity.

The leptin receptor gene, unlike the leptin gene, is highly polymorphic. In the leptin receptor gene, various single nucleotide exchange polymorphisms have been described. Some studies have shown that the Q223R polymorphism is associated with BMI, overweight status and obesity.^(40,50,59) However, its relationship with smoking and body weight has not been yet reported, although an association between Q223R polymorphism and the increase in the BMI of Caucasian nonsmoking patients has been found.⁽⁴⁹⁾

Final considerations

In view of these facts, the following considerations can be enumerated:

- 1) There is an inverse relationship between smoking and body weight/BMI, and this relationship is dose-dependent, that is, BMI

decreases in parallel with an increase in the number of cigarettes consumed;

- 2) Smoking cessation, in most cases, causes weight gain at the beginning of the process, and this weight gain is more significant in females;
- 3) Weight gain can be a risk factor for the smoking cessation failure, principally in females;
- 4) Even if the mechanisms of the inverse relationship smoking/BMI are not totally clear, there is evidence that, during the process of smoking cessation, there is a change in lipid metabolism, with greater fat storage and less fat oxidation;
- 5) Nicotine seems to be the primary agent involved in these phenomena due to its effect on certain neurotransmitters that act in the control and regulation of appetite and satiety in the hypothalamus;
- 6) Genetic modifications might be implicated in these events, and some preliminary studies have suggested that polymorphisms that regulate leptin or leptin receptors are implicated;
- 7) The relationship between the leptin-ghrelin-NPY system, which regulates satiety/hunger, and smoking/smoking cessation is still controversial, and its actual role might be secondary to, and not the cause of, changes in body weight;
- 8) Nicotine replacement therapy, whether used in combination with bupropion or not, has shown satisfactory results in weight control during smoking cessation; and
- 9) There is no clear, definitive evidence relating smoking or smoking cessation to changes in body weight by means of genetics, although there is evidence that this is a promising line of research.

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