Review

Adiponectin and Smoking Status: A Systematic Review

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Aim: Smoking and adiponectin are individually associated with cardiometabolic pathologies. The present systematic review was carried out in order to summarize the association between the smoking status and circulating adiponectin levels.

Methods: Original articles, restricted to epidemiological studies (by a cross-sectional, case-control and cohort study design) and intervention studies for adult humans, were screened for the years 1995-2010. All of the research group members then selected the eligible literature and assessed the articles in a structured systematic review manner.

Results: There were 11 key studies, which included 9 articles with a cross-sectional design and 2 articles with an intervention design. Most cross-sectional studies reported lower levels of adiponectin in current smokers than in non/never smokers and/or ex-smokers, while 2 studies reported a non-significant difference in adiponectin between male smokers and non-smokers. The two intervention studies, conducted in patients on 9-week bupropion treatment and 6-month non-pharmacological treatment, reported that smoking cessation increased the adiponectin levels.

Conclusion: This review suggests that there is a decreased adiponectin level in current smokers and this reduction can be reversed by quitting smoking. More studies are required to confirm the findings and elucidate the biological mechanisms underlying the association between the smoking status and adiponectin levels.


Key words: Adipocytokine, Tobacco, Nicotine, Lifestyle

Introduction

The health risks of tobacco smoking have been established for decades worldwide, and regulating smoking remains a public health challenge1-3). Smoking is a well-known atherosclerotic risk factor, although the underlying mechanisms are complex and incompletely clarified1-3). On the other hand, metabolic syndrome has recently been given sociomedical attention due to its increasing prevalence and atherosclerotic burden4, 5). Of note, smoking is reportedly associated with the development of metabolic syndrome, presumably via a pathway leading to the development of cardiovascular disease6-9).

Metabolic syndrome is an obesity-related disorder, and various adipocytokines play crucial roles in the pathophysiology of metabolic syndrome10). In particular, adiponectin is a key protein secreted by adipocytes, which can contribute to improving cardiometabolic outcomes11, 12). Namely, a decrease in the circulating adiponectin concentration is reported to be associated with cardiometabolic disorders11, 12); there-
As the first step, all candidate bibliographies that were searched were screened according to the title and abstract by at least two researchers: one researcher checked the appropriateness of publications independently of another researcher, and subsequently, the compatibility between the two researchers was confirmed. When the researchers’ opinions matched, the articles were considered to be eligible for the next step or were omitted. If the researchers’ opinions did not match, the eligibility of articles was determined during a discussion. In this step, the literature was restricted to epidemiological studies (by a cross-sectional, case-control and cohort study design) and intervention studies. Only original articles focusing on the association between smoking and adiponectin were considered as appropriate publication types. As the study populations, when there were the studies of pregnant subjects and those with specific disease conditions such as severe cardiopulmonary disease, psychological disease or collagen disorders, the articles were excluded.

As the second step, the text contents of the articles were assessed using a sheet according to the following terms of the study: the study’s aim, subjects, methodologies (i.e., the regulation of bias and confounding factors, statistical analysis) and the presenta-
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from the US 21). Even though there appeared to be relatively many studies in Asian populations, similar trends were observed in the association between smoking and adiponectin across countries.

Measures of Interests

The total adiponectin levels in the circulation were measured in 10 studies. While high-molecular-weight adiponectin in the circulation was used in one study 14), this report was included in the present systematic review because the high-molecular-weight type is currently considered an active form of adiponectin 25). The smoking status was assessed mainly by questionnaire methods, while one study simultaneously used an objective measure to evaluate the smoking exposure (e.g., cotinine 15).

Study Designs

A cross-sectional design was applied in 9 studies 14, 17-24), and an intervention design was used in the other 2 studies 15, 16). The intervention studies used the following treatment: a 9-week pharmacological approach (150 mg sustained-release bupropion twice daily) for non-specific subjects 15) and a 6-month non-pharmacological approach to quit smoking for patients with stable angina pectoris 16). While most of the cross-sectional studies were conducted in healthy and non-specific diseased populations recruited from general health check-ups or advertisements for the study participation 14, 17-20, 22-24), only one study focused on patients with coronary artery disease 21).

Gender Differences

Except for 2 studies 15, 22), 7 studies (including one intervention study) reported the results for males only 14, 16, 17, 19, 21, 23, 24) and 2 studies reported the results separately for males and females 18, 20). Although there were only a few studies of females, similar trends were observed in the association between smoking and adiponectin in both genders.

Smoking-Related Information

A few studies assessed the detailed information on smoking habits such as non/never, ex- and current smoking, as well as the amount and duration smoked. A linear trend of adiponectin from high to low levels, corresponding to non/never, ex- to current smokers, was reported 17, 20, 21, 23). Most studies revealed that the adiponectin levels in non/never and ex-smokers were relatively high compared to current smokers 17, 20, 23) while, in one study, the adiponectin levels were lower in non/never, current and ex-smokers, in that order 21). In terms of smoking intensity, the adiponectin levels
Table 1. Summary of the association between smoking and adiponectin levels

<table>
<thead>
<tr>
<th>Authors</th>
<th>Publication Year</th>
<th>Subject number (male/female)</th>
<th>Country</th>
<th>Adiponectin in smokers</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Adiponectin (μg/mL)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional studies</td>
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<td></td>
</tr>
<tr>
<td>Kawamoto R14, * #</td>
<td>2010</td>
<td>747</td>
<td>Japan</td>
<td>↓</td>
<td>Never 64 (12)</td>
<td>Never 23.6 (2.9)</td>
<td>Never 0.58</td>
<td>Adiponectin: mean log-HMW level. Other lifestyle variable considered: drinking.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ex 65 (13)</td>
<td>Ex 23.8 (2.9)</td>
<td>Ex 0.59</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Light 45 (15)</td>
<td>Light 23.0 (3.3)</td>
<td>Light 0.48</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Heavy 59 (11)</td>
<td>Heavy 23.2 (3.1)</td>
<td>Heavy 0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sull JW17, #</td>
<td>2009</td>
<td>2500</td>
<td>Korea</td>
<td>↓</td>
<td>Non 44.5 (8.8)</td>
<td>Non 24.6 (2.4)</td>
<td>Non 7.3 (4.4)</td>
<td>Other variable considered: drinking.</td>
</tr>
<tr>
<td></td>
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<td>Ex 46.8 (9.1)</td>
<td>Ex 24.6 (2.4)</td>
<td>Ex 7.0 (3.8)</td>
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<td></td>
<td>Current 42.8 (7.9)</td>
<td>Current 24.4 (2.8)</td>
<td>Current 6.6 (3.7)</td>
<td></td>
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<tr>
<td>Ahonen TM18, #</td>
<td>2008</td>
<td>841 (365/476)</td>
<td>Finland</td>
<td>△</td>
<td>Male Non 47 (6)</td>
<td>Female Non 26.5 (3.1)</td>
<td>Male</td>
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<td></td>
<td>Daily 46 (7)</td>
<td>Daily 26.1 (3.8)</td>
<td>Daily 26.6 (3.8)</td>
<td>Female</td>
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<td></td>
<td></td>
<td></td>
<td>Female Non 47 (6)</td>
<td>Female 26.4 (4.8)</td>
<td>Female 8.2 (4.72)</td>
<td>Female</td>
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<td></td>
<td>Daily 45 (6)</td>
<td>Daily 25.8 (4.8)</td>
<td>Daily 6.94 (3.27)</td>
<td></td>
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</tr>
<tr>
<td>Jang Y19</td>
<td>2007</td>
<td>480</td>
<td>Korea</td>
<td>△</td>
<td>Male Non 51.8 [0.49]</td>
<td>Regular 54.0 [0.55]</td>
<td>Male 5.00 [0.17]</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Regular 42.4 [0.19]</td>
<td>Regular 24.4 [0.19]</td>
<td>Regular 5.8 [0.11]</td>
<td>Regular 4.80 [0.18]</td>
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<td></td>
<td>Ex 49.8 (6.6)</td>
<td>Ex 23.4 (2.7)</td>
<td>Ex 5.99</td>
<td>Current 5.87</td>
<td></td>
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<td></td>
<td>Current 48.8 (6.7)</td>
<td>Current 23.0 (2.7)</td>
<td>Female 26.6 (3.8)</td>
<td>Female</td>
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<td></td>
<td></td>
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<td></td>
<td>Female Never 46.2 (7.0)</td>
<td>Female 21.7 (2.9)</td>
<td>Female 9.93</td>
<td>Female</td>
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<td></td>
<td></td>
<td>Ex 45.2 (5.7)</td>
<td>Ex 22.2 (2.4)</td>
<td>Ex 9.49</td>
<td>Female</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Current 46.9 (6.6)</td>
<td>Current 22.4 (3.5)</td>
<td>Male 7.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim OY21, #</td>
<td>2006</td>
<td>613</td>
<td>Korea</td>
<td>↓</td>
<td>Never 54.8 [0.76]</td>
<td>Never 24.6 [0.23]</td>
<td>Never 5.07 [0.30]</td>
<td>Other variable considered: drinking.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Ex 54.7 [0.70]</td>
<td>Ex 25.3 [0.27]</td>
<td>Ex 3.75 [0.20]</td>
<td></td>
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<td></td>
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<td></td>
<td>Current 54.4 [0.41]</td>
<td>Current 25.1 [0.13]</td>
<td>Current 4.14 [0.12]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbasi F22, *</td>
<td>2006</td>
<td>60 (27/30)</td>
<td>USA</td>
<td>↓</td>
<td>Insulin resistant Non 51 (10)</td>
<td>Insulin resistant Non 28.0 (2.0)</td>
<td>All subjects</td>
<td>ADIPOnectin: geometric mean level.</td>
</tr>
<tr>
<td></td>
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<td>Current 52 (9)</td>
<td>Current 28.2 (2.9)</td>
<td>Current 11.7</td>
<td>Current 8.6</td>
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<td>Insulin sensitive Non 52 (7)</td>
<td>Insulin sensitive Non 27.3 (2.1)</td>
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<td>Current 49 (6)</td>
<td>Current 26.7 (3.1)</td>
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</tbody>
</table>
(Cont Table 1)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Subject number (male/female)</th>
<th>Adiponectin in smokers</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Adiponectin (µg/mL)</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Both</td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iwashima Y23, * , # 2005</td>
<td>331</td>
<td>Japan</td>
<td>↓</td>
<td>Never 58.0 [1.2]</td>
<td>Never 23.6 [0.3]</td>
<td>Never 6.5 [0.4]</td>
<td>Other variable considered: drinking.</td>
<td></td>
</tr>
<tr>
<td>Tsukinoki R24, * , # 2005</td>
<td>195</td>
<td>Japan</td>
<td>↓</td>
<td>at baseline 42.0 (10.3)</td>
<td>at baseline 23.6 (2.8)</td>
<td>at baseline 4.9 (2.2)</td>
<td>At baseline: 202 subjects included. Other variables considered: drinking, dietary and exercise.</td>
<td></td>
</tr>
<tr>
<td>Efstathiou SP15, * 2009</td>
<td>110</td>
<td>Greek</td>
<td>↑</td>
<td>Non-quitters 43.4 (12.1)</td>
<td>Quitters 46.0 (13.2)</td>
<td>Before intervention</td>
<td>9-week bupropion intervention. Fasting glucose (mmol/L): Before intervention Non-quitters 5.2 (0.4) Quitters 5.1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Otsuka F16, * 2009</td>
<td>72</td>
<td>Japan</td>
<td>↑</td>
<td>Persistent 66.5 (7.2)</td>
<td>Quitters 68.3 (7.0)</td>
<td>Before intervention</td>
<td>Adiponectin: median level. 6-month non-pharmacological intervention. Hemoglobin A1c (%): Before intervention Persistent 5.7 (0.6) Quitters 5.6 (0.5)</td>
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</tr>
</tbody>
</table>

BMI: body mass index, HMW: high-molecular weight. ↑: high/increase, ↓: low, Δ: non-specific difference.
The data for age, BMI and adiponectin are presented as the mean ± (standard deviation) or [standard error].
*number*: cited reference number. *: study of Japanese subjects. *age- and BMI-adjusted analysis was conducted. The smoking status was based on the expression of each article.
in non/never, ex- and light smokers were higher relative to the levels in heavy smokers and, in other studies, the adiponectin levels tended to be lower in heavy smokers relative to light smokers among current male smokers who had lower adiponectin levels than non/never or ex-smokers. Another study also reported that although the Brinkman index was not associated with the adiponectin levels, the number of cigarettes smoked per day was inversely associated with the adiponectin levels among current smokers. An additional study reported that men who had quit smoking for more than 20 years and women for 10 years could have adiponectin levels similar to those observed in nonsmokers.

Other Lifestyle-Related Factors

Since not only smoking, but also other lifestyle-related factors, can affect adiponectin levels, several studies took other lifestyle-related factors into account, such as dietary components (e.g., vegetable intake, eating-out habits, energy intake), alcohol consumption, and exercise. There were several studies where obesity-related traits such as body mass index were included as an adjusted variable in the analysis model; however, even when these factors were considered in the analyses, the relationship between smoking and adiponectin was not largely affected. In addition to the obesity-related traits, when subject age was also adjusted in the analyses, the relationship between smoking and adiponectin remained unaffected.

Level of Evidence

Although intervention studies were included in the reviewed articles, these studies were basically of a single-arm group. There were no studies corresponding to randomized controlled trials, well-designated controlled trials, well-designated cohort studies, case-control analytical studies, or studies showing marked changes in some outcomes. The evidence for the reviewed articles was thus considered to be at level 3.

Discussion

The present review demonstrated, as a whole that, 1) there is a lower adiponectin level in current smokers relative to non/never smokers and/or ex-smokers, with a possible dose-response relationship, and 2) there is a possible reversibility of this association after smoking cessation. Although basic confounders such as age and obesity-related traits, in addition to other lifestyle-related factors, can potentially affect adiponectin levels, several studies revealed that the adjustments for these factors did not largely change our present findings. Accordingly, even though there were limited published articles and/or no randomized control trials focusing on the association between the smoking status and adiponectin levels (thus, the level of evidence for the present review was not very high), it is valuable to note that relatively consistent data have been reported.

These findings may suggest important clinical implications. There are currently no reports showing that the modulation of adiponectin, resulting from the modification of smoking habits, affects the development of metabolic syndrome, atherosclerosis and cardiovascular disease; however, smoking habits are modifiable, so it is expected that smoking cessation can prevent future negative cardiometabolic outcomes by increasing the adiponectin levels.

Several biological reasons for the lower adiponectin levels by smoking are considered in the present review. Nicotine itself inhibits the expression of the adiponectin gene in adipocytes. Smoking also provokes oxidative stress and inflammatory cytokines (i.e., tumor necrosis factor-alpha), especially by which the expression of adiponectin gene is inhibited. Smoking is known to impair vessel walls, and adiponectin can accumulate in these walls; therefore, adiponectin levels may be reduced in the circulation due to their enhanced consumption by the vessel walls. In our present review, significant relationships between smoking and adiponectin were unaffected even after adjusting for obesity-related traits in the analyses. This could support the presence of mechanisms regarding not only adipose tissues, but also other tissues, including vessel walls. We think that both the nicotine and smoking-induced pathways may directly and indirectly be associated with low adiponectin levels in smokers.

In addition, smoking cessation through intervention promptly induced increases in adiponectin levels. This result may indicate a mechanistically rapid response to smoking exposure. Whereas most studies reported lower adiponectin levels in current smokers than in ex-smokers, one cross-sectional study reported lower adiponectin levels in ex-smokers than in current smokers. This may also imply the presence of a slow response to the reversibility of the reduced adiponectin levels. In one study demonstrating a non-significant difference in adiponectin levels between smokers and nonsmokers, the nonsmokers included those who had quit at least 6 months prior. There can be a continued influence of the smoking status on adiponectin levels after quitting smoking. If there is a slow reversibility of adiponectin levels, this may support the presence of mechanisms regarding not only adipose tissues, but also other tissues, including vessel walls. We think that both the nicotine and smoking-induced pathways may directly and indirectly be associated with low adiponectin levels in smokers.
tin levels after smoking cessation, the definition of ‘nonsmokers’ by the study may make a difference in the adiponectin levels. Further research is warranted to clarify the deeper mechanism(s) underlying the association between smoking and adiponectin.

Our study had several limitations. Most reviewed studies evaluated the smoking status on the basis of questionnaires, not objective measures, although this methodology is often used in this research field. The categories of the smoking status were not always identical between studies. Most studies did not include information about the Brinkman index and the duration of smoking. The assay system used to measure the circulating adiponectin levels could also be different among studies; thus, the consistency of the findings should be given some consideration. Moreover, the follow-up periods of only 2 intervention studies reviewed \(^{15,16}\) were short. Smoking cessation can cause weight gain and/or glucose intolerance \(^{34,36}\). Such changes of metabolic parameters as body mass index, glucose and hemoglobin A1c were not reported during the study period of the 2 interventions (as shown in Table 1). One intervention study reported that changes in glucose and obesity-related traits were not significantly correlated with the change in adiponectin levels in multivariate-adjusted analysis \(^{15}\) and another intervention study reported that changes in glucose and obesity-related traits were not extracted as variables significantly correlated with the change in adiponectin levels in the model of multivariate-adjusted analysis \(^{16}\); however, longer follow-up studies remain necessary to determine the effect of smoking cessation on adiponectin. In addition, studies with adjustments for various factors affecting the smoking status and adiponectin levels were limited. Although similar trends were likely observed in the association between smoking and adiponectin in men and women, there are only a few studies of women to define the gender difference in their association. These issues must be addressed in future work.

In summary, the present systematic review suggests that there is a lower adiponectin level in current smokers relative to non/never smokers and smoking cessation can increase adiponectin levels. Further studies are needed to confirm these findings and to elucidate the biological mechanisms underlying the relationship.

**Competing Interests**

The authors declare that they have no competing interests. Dr. Nakamura has consulted pharmaceutical companies, but only regarding the findings of clinical trials on medications for tobacco dependence treatments.

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