Circulating leptin and adiponectin levels in patients with pancreatic cancer

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To the Editor: The etiology and the pathogenesis of pancreatic cancer (PC) are poorly understood. It has long been recognized that various intertwined factors, including genetic susceptibility and environmental stimuli (such as cigarettes, diabetes mellitus, and adiposity), are potential risk factors for high morbidity and mortality in PC patients.[1] The regulatory role of adipokines in the pathogenesis of tumors remains controversial. It has been generally accepted that obesity-related conditions increase susceptibility to various tumors, including PC. PC patients with increased adiposity have a heightened risk for poorer prognosis and higher mortality, which suggests that the significance of obesity-related factors (ie, leptin and AdipoQ) in the onset and/or development of PC is becoming increasingly prominent. However, circulating leptin and AdipoQ levels in PC compared with those in non-PC individuals remain controversial. Hence, we sought to perform a meta-analysis to settle the issues in dispute.

This meta-analysis was conducted based on the principles of MOOSE and PRISMA. A predefined protocol was registered on the PROSPERO platform (No. CRD42020178522). We comprehensively searched the PubMed, Embase, and Cochrane databases (deadline: April 2020). Eligibility criteria are shown in Supplementary File 1, http://links.lww.com/CM9/A555. The Newcastle-Ottawa scale was selected to assess the quality of our included studies, which was similar to the method used in our previously published articles to evaluate the quality of the included studies.[2] We applied Stata (ver. 14.0) software to conduct all statistical analyses. The specific statistical principles are shown in Supplementary File 2, http://links.lww.com/CM9/A555.

The selection workflow of the involved study is shown in Supplementary Figure 1, http://links.lww.com/CM9/A554. The primary information of the included studies is summarized in Supplementary File 3, http://links.lww.com/CM9/A555. A total of 17 articles (involving 20 subgroups) with approximately 6000 participants evaluated circulating leptin levels in patients with PC compared with those without PC, and the pooled data revealed that circulating leptin levels were significantly lower in patients with PC than in those without PC (standardized mean difference [SMD] = −0.923, 95% confidence interval [CI] [−1.290 to −0.556], $P < 0.001$) [Figure 1A]. Fourteen articles (involving 17 subgroups) evaluated circulating AdipoQ levels in patients with PC compared with those without PC, with the pooled data indicating that higher AdipoQ levels were observed in PC patients (SMD = 0.830, 95% CI [0.497–1.164], $P < 0.001$) [Figure 1B]. The results of the subgroup analysis for circulating leptin and AdipoQ levels are shown in Supplementary File 4, http://links.lww.com/CM9/A555.

Cachexia and diabetes are the two most important clinical issues in patients with PC. We analyzed whether there were differences in peripheral blood leptin and adiponectin levels in patients with different states of PC. A total of seven studies compared circulating leptin levels between PC patients with cachexia and without cachexia, with the pooled results revealing a significantly decreased leptin level in PC patients with cachexia [Supplementary Figure 2A, http://links.lww.com/CM9/A554]. Three studies compared circulating leptin levels between PC patients with and without diabetes, with the pooled data showing a trend toward a lower leptin level in the diabetes group that did not achieve statistical significance [Supplementary Figure 2B, http://links.lww.com/CM9/A554]. Several studies investigated the association of AdipoQ levels with

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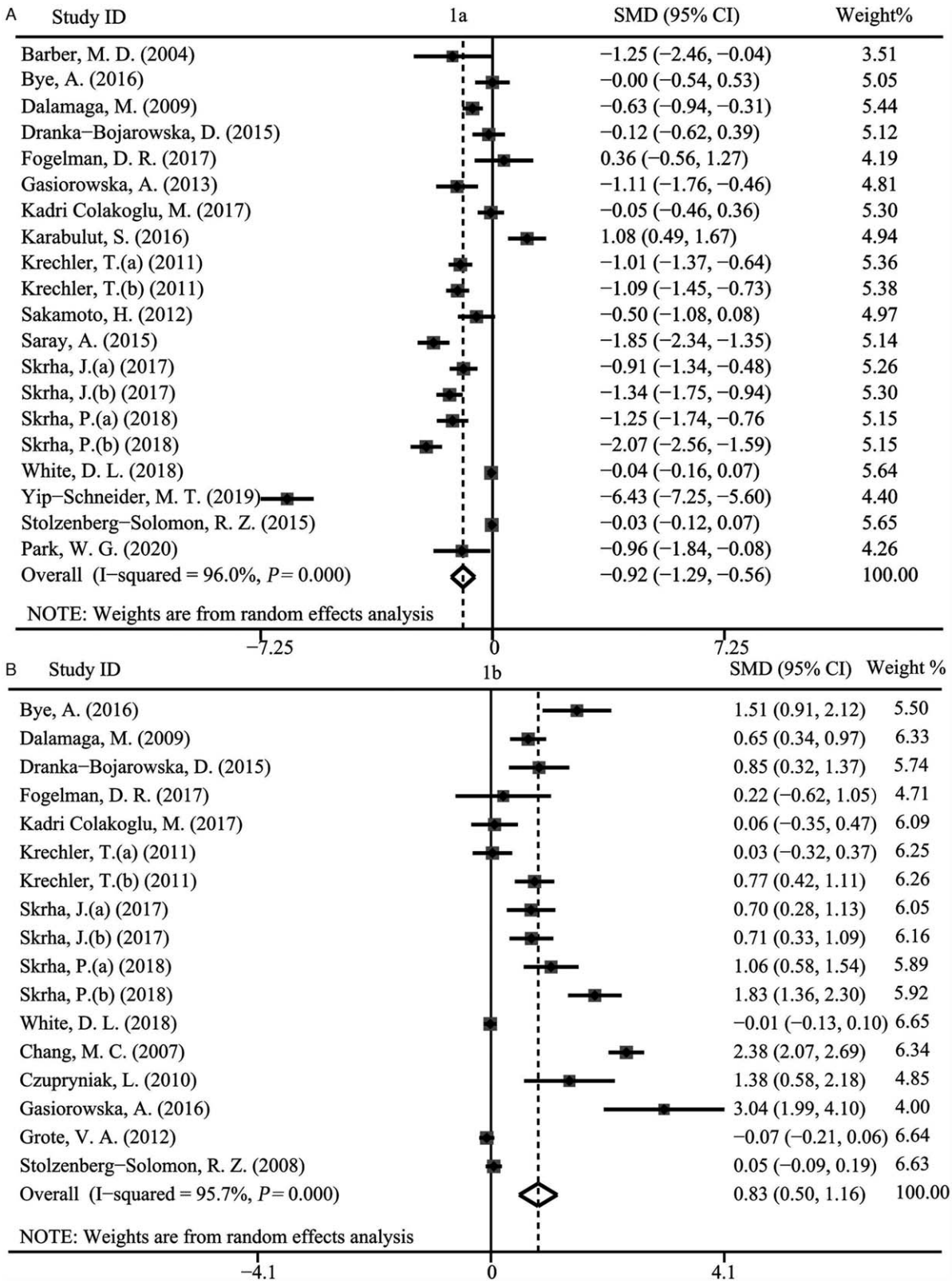

Figure 1: Association of circulating leptin and AdipoQ levels with the occurrence of PC. Circulating leptin (A) and AdipoQ (B) levels in PC patients compared with non-PC individuals. PC: Pancreatic cancer; SMD: Standardized mean difference.

cachexia and diabetes in PC patients, with pooled data showing no significant difference [Supplementary Figure 2C and 2D, http://links.lww.com/CM9/A554].

To better explore the potential association between leptin, AdipoQ, and PC, we also investigated the differential expression levels of circulating leptin and AdipoQ between

PC and precancerous lesions. A total of six studies compared circulating leptin levels between PC and precancerous lesions, and the pooled data showed a significantly lower leptin level in the PC group [Supplementary Figure 3A, http://links.lww.com/CM9/A554]. Subgroup analysis by type of precancerous lesions showed a significantly lower leptin level in PC patients than in patients with pancreatic intrapapillary mucinous neoplasm and autoimmune pancreatitis but not in patients with chronic pancreatitis [Supplementary Figure 3A, http://links.lww.com/CM9/A554]. Six studies compared circulating AdipoQ levels between PC and precancerous lesions, and the combined results revealed a significantly higher AdipoQ level in the PC group [Supplementary Figure 3B, http://links.lww.com/CM9/A554]. A further subgroup analysis regarding chronic pancreatitis was performed, and the pooled data indicated a significantly higher AdipoQ level in PC patients than in chronic pancreatitis patients [Supplementary Figure 3B, http://links.lww.com/CM9/A554].

Although our results have resolved the long-standing dispute about peripheral blood leptin and adiponectin levels in patients with PC, the heterogeneity of the results is significant. Therefore, next, we sought to explore the possible sources of heterogeneity and the existence of publication bias through meta-regression analyses, sensitivity analyses, and funnel plots. The results of meta-regression analyses demonstrated that the heterogeneity of leptin levels was primarily attributable to the source of leptin ($P = 0.039$), assay method ($P = 0.034$), and body mass index (BMI) ($P = 0.029$) rather than ethnicity ($P = 0.115$), sample size ($P = 0.662$), source of control ($P = 0.233$), or method of control ($P = 0.688$). Regarding AdipoQ levels, the heterogeneity was attributable only to the source of control ($P < 0.001$) and not to ethnicity ($P = 0.670$), source of AdipoQ ($P = 0.998$), sample size ($P = 0.995$), assay method ($P = 0.721$), method of control ($P = 0.515$), or BMI ($P = 0.646$). The results of sensitivity analyses revealed no substantial change in the pooled data regarding leptin levels [Supplementary Figure 4A, http://links.lww.com/CM9/A554] and AdipoQ levels [Supplementary Figure 4B, http://links.lww.com/CM9/A554], indicating that our results were relatively robust. Funnel plots of circulating leptin and AdipoQ levels were used to evaluate publication bias. Through the visual inspection of the funnel plots, there were obvious asymmetries that indicated a possibility of publication bias, which were not supported by Begg regression tests (leptin: $P = 0.820$ [Supplementary Figure 4C, http://links.lww.com/CM9/A554]; AdipoQ: $P = 0.064$ [Supplementary Figure 4D, http://links.lww.com/CM9/A554]); therefore, further verification by trim and fill funnel plots was employed to adjust for potential publication bias. However, the pooled data regarding leptin that had been significant before the adjustment with the "trim and fill" method remained significant after the adjustment (SMD = −1.548, 95% CI [−2.162 to −0.933], $P < 0.001$) [Supplementary Figure 4E, http://links.lww.com/CM9/A554], indicating that this publication bias did not impact the pooled estimates. For AdipoQ, the results of the "trim and fill" method revealed that no trimming was performed, and the data were unchanged [Supplementary Figure 4F, http://links.lww.com/CM9/A554], suggesting that there was no significant publication bias.

As outlined above, significantly decreased circulating leptin levels and increased circulating AdipoQ levels were observed for PC patients compared with non-PC individuals. PC patients with cachexia showed a significantly lower leptin level than those without cachexia. Compared to patients with pancreatic intrapapillary mucinous neoplasm and autoimmune pancreatitis, PC patients showed a significantly lower leptin level. Compared to patients with chronic pancreatitis, PC patients showed a significantly elevated AdipoQ level. These findings not only have resolved disputes regarding circulating leptin and AdipoQ levels in PC patients, but also provide new information regarding the pathogenesis of PC. Despite important findings, our research has some inevitable limitations that should be considered, which was shown in Supplementary File 5, http://links.lww.com/CM9/A555.

Registration number

A predefined protocol was registered in the platform of INPLASY (No. INPLASY202040138) and PROSPERO (No. CRD42020178522).

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Conflicts of interest

None.

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