 Editorial

Could Dirty Air Cause Diabetes?

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Diabetes is a growing epidemic, and it has become arguably one of the biggest health challenges of our time. Currently, more than 23 million Americans have diabetes, and the Centers for Disease Control and Prevention estimate that in the last 15 years, the number of people in the United States with diabetes has more than doubled. Diabetes is increasing at an alarming rate in Europe as well, and it is fast becoming a major health threat in developing countries such as India and China. Despite its high prevalence, however, diabetes remains somewhat of a mystery. Although type 1 diabetes mellitus could be attributed to insufficient insulin release by the β-cells of the pancreas, the origins of type 2 diabetes mellitus (which accounts for >90% of the cases of diabetes) remain obscure. Insulin resistance is a cardinal feature of type 2 diabetes mellitus; however, it is not clear how whole-body insulin resistance develops, which specific tissues are affected first and which ones later, and how metabolic changes in individual tissues contribute to the overall development of the disease and its many secondary complications.

The origin of diabetes is equally complex. Although diabetes develops in genetically susceptible individuals, it is a complex trait and does not show simple mendelian inheritance. Because the rates of diabetes change with the environment in several population groups, it has been suggested that modifiable environmental factors and lifestyle choices account for more than 90% of adult-onset diabetes. Nevertheless, our understanding of the environmental causes of diabetes has remained rather rudimentary, being limited mostly to the impact of physical inactivity or unhealthy dietary choices. In this context, the study by Sun and coworkers published in the present issue of Circulation is interesting because it provides new evidence showing that exposure to particulate air pollution increases blood glucose, visceral adiposity, and insulin resistance in high-fat–fed mice. These results raise the possibility that exposure to air pollution may be a new and heretofore unrecognized contributing factor to the development of diabetes, and they strengthen the rationale for studying the link between air pollution and diabetes in human populations. Indeed, Brook et al1 have recently reported that exposure to NO2, a maker of traffic-related air pollution, is positively associated with the prevalence of diabetes in women.

A large body of evidence, accumulated over the last decade, suggests that exposure to air pollution has adverse health effects. Long-term studies have shown that individuals living in polluted cities have a lower life expectancy and are more likely to die earlier than those living in less polluted areas. Further analysis revealed that such mortality is mostly due to cardiovascular disease and is strongly associated with an increase in air particulate matter (PM). Ambient air contains a range of particles that vary in size over 5 orders of magnitude (from 0.001 to 100 μm). Larger particles (>10 μm; PM10) are derived from windblown soil or dust or volcanic activity and often consist of sea salts, pollen, mold, and spores. Such particles are also generated by human activities such as mining or agriculture. Fine particles (0.1 to 2.5 μm; PM1–2.5) are generated from combustion emissions such as automobile exhaust or wood or coal burning and industrial emissions from smelters, paper and steel mills, or cement plants. Because fine and ultrafine (<2.5 μm) particles penetrate deeper in the lung and could potentially appear in the circulation, they are considered to be of greater health significance. Several time-series analysis studies show a consistent association between PM10 and PM2.5 levels and daily mortality due to myocardial infarctions, arrhythmias, and heart failure. Although the link is largely statistical, studies showing that even a short-term decrease in air pollution is associated with a decrease in area deaths argue in favor of a causal relationship between PM exposure and mortality. The most striking examples are provided by studies from Utah, where a 13-month closure of a local steel mill led to a significant (3.2%) decrease in mortality, and studies from Dublin, which showed that a decrease in PM due to a ban on coal was associated with a 5.7% decrease in all-cause death rates. Such data showing a large decrease in death after a reduction in air pollution within a few weeks to years provide a natural control for other variables and bolster the hypothesis that long-term exposure to particulate air pollution has lasting health effects.

Experiments with animal models suggest plausible mechanisms by which PM exposure could chronically impair cardiovascular health and trigger acute clinical events. Previous studies from Sun and associates4 have shown that a 6-month exposure to concentrated PM1–2.5 led to a 1.5-fold increase in atherosclerotic lesion formation in apolipoprotein E–null mice. In this model, exposure to PM not only increased atherogenesis, it also induced endothelial dysfunction and vascular inflammation. In the current study, Sun and associates2 expand their earlier observations and show that in high-fat–fed nonatherosclerotic C57 mice, a 6-month PM2.5...
exposure, at cumulative levels likely to be encountered in many US cities, induces whole-body insulin resistance. This increase in insulin resistance was accompanied by changes in insulin signaling and an increase in macrophage accumulation in adipose tissue. The authors suggest that PM$_{2.5}$ exacerbates insulin resistance by enhancing inflammation in adipose tissue at the level of adipose tissue macrophages. Interestingly, exposure to PM$_{2.5}$ altered the balance between M1 and M2 macrophages in adipose tissues. Given the extensive evidence supporting the view that an increase in adipose inflammation is an important determinant of insulin resistance, it appears that an increase in M1 macrophages in the adipose tissue of PM-exposed mice may provide one mechanism by which PM increases insulin resistance.

The white adipose tissue is considered to be a depot of energy storage, and it accounts for 5% to 15% of the oral glucose load. Recent work has led to the realization that the adipocyte is a major endocrine organ and that it secretes factors that play an important role in appetite regulation and energy homeostasis. Deletion of insulin receptor in fat cells in mice, however, results in slightly improved glucose and lipid homeostasis and an increase in insulin sensitivity. Although the mechanisms underlying the paradoxical effects of insulin receptor deletion in adipocytes are unclear, it has been suggested that deletion of the insulin receptor in adipocytes increases adiponectin and leptin levels and decreases tumor necrosis factor-α expression in fat. In contrast, in PM$_{2.5}$-exposed mice, the plasma concentrations of tumor necrosis factor-α and adipokines were increased, which suggests that PM$_{2.5}$ exposure does not exclusively affect adipocytes and that insulin resistance and glucose intolerance in these mice may be secondary to inflammatory changes that lead to greater leukocyte adhesion and vascular dysfunction. Nevertheless, the presence of activated macrophages in adipose tissue of PM-exposed mice suggests that exposure to pollutants can regulate appetite and energy homeostasis and thereby increase whole-body insulin resistance.

Systemic effects of PM on insulin resistance in animal models are consistent with epidemiological data showing that humans exposed to high levels of PM have higher levels of plasma interleukin-6 or C-reactive protein. It is likely that inflammation is initiated in the lung and then spreads to other tissues. Although this remains to be shown, a recent study reported that exposure to ultrafine PM increases the expression of antioxidant genes in the liver of apolipoprotein E–null mice, which indicates that the effects of PM are likely to be widespread, involving several organ systems. Such systemic responses could provide one explanation of why the effects of inhaled pollutants are not restricted to the lung and why exposure to PM is associated with high levels of cardiovascular mortality, independent of lung disease.

In addition to mediating the effects of air pollution, inflammation may also be an important determinant of susceptibility. Several studies have shown that individuals with chronically elevated levels of low-grade inflammation, such as those with preexisting heart disease, hypertension, diabetes, or metabolic syndrome or individuals who are old, obese, or smokers, are more susceptible to PM. Within these conditions, diabetes and obesity may represent a specific subset of susceptibility states. In the current study, Sun et al found that PM$_{2.5}$ exposure did not affect insulin resistance in lean mice. This is in agreement with their previous work showing that PM exposure enhances lesion formation only in apolipoprotein E–null mice on high-fat diets, not in those on a normal chow diet. Collectively, these results suggest that the effects of pollution develop more strongly over a background of obesity. Corresponding human data are in agreement. In a study on postmenopausal women, the relative risk for incident cardiovascular disease associated with long-term ambient PM$_{2.5}$ was found to increase with increasing levels of obesity. Although specific reasons for the high sensitivity of obese individuals to PM remain unclear, it may be that persons with higher body mass index simply absorb more particles owing to greater lung area or a greater deposition of fine particles in the lung, and therefore, they are at a greater risk than lean persons. There may be additional reasons, but to identify them, we need a better understanding of the nature and the mechanism of particle toxicity. Extensive research in this area has shown that exposure to particulate air pollution elicits a variety of responses that range from a decrease in heart rate variability and endothelial function to an increase in thrombosis and atherogenesis. Yet it remains unclear how these responses are triggered, how they are related to each other, and how they contribute to the development of diabetes and obesity. Clearly, much work remains to be done to move the field forward from descriptive understanding to a mechanistic explanation of the phenomenon.

Pollutants other than air particulates have also been shown to exacerbate insulin resistance and diabetes. In a recent study, Navas-Acien and coworkers found that in a population exposed to low to moderate arsenic levels in the United States, there was a positive association between urine arsenic levels and the prevalence of type 2 diabetes mellitus. This study corroborates extensive data collected previously from exposed populations in Taiwan, Bangladesh, and Mexico that show that chronic exposure to high levels of arsenic in drinking water is associated with a higher incidence of diabetes. The striking diabetogenic effect of arsenic, albeit at high concentrations, has been demonstrated in animal models as well. It is possible that both arsenic and PM engage similar mechanisms and that the increase in insulin resistance in arsenic-exposed populations is also a result of chronic low-grade inflammation.

Endocrine disruptors are another class of common pollutants that have been linked to the development of obesity and insulin resistance. Pollutants such as phthalates, diethylstilbestrol, and bisphenol A can perturb adipocyte biology, and it has been reported recently that exposure of human tissues to bisphenol A (a monomer of polycarbonate plastic) at environmentally relevant concentrations inhibits the release of adiponectin, an important adipokine that increases insulin sensitivity and reduces tissue inflammation. Because human exposure to pollutants such as bisphenol A, arsenic, and air particulates is widespread and frequent, it may be worth considering that the current burden of diabetes and the recent explosion of obesity may be attributable in part to living in polluted environments.
The association between pollution and diabetes suggested by Sun et al. has significant public health implications and raises important questions regarding urbanization, diabetes, and obesity. Are obesity and diabetes outcomes of repeated and chronic exposure to pollution? Which individuals are likely to be most affected? To what extent does pollution contribute to the current explosion in diabetes and obesity in the developed and the developing world? Can we prevent diabetes by controlling the levels of pollution? Which individuals are likely to be most affected? To what extent does pollution contribute to the current explosion in diabetes and obesity in the developed and the developing world? Can we prevent diabetes by controlling the levels of pollution? And if so, which of the thousands of chemicals in PM should be regulated? Clearly, future studies in this area are likely to address these issues, but the work done so far is beginning to change our perception of metabolic diseases such as diabetes. A long-held view was that conditions such as obesity and diabetes arise from a mismatch between dietary intake and nutrient requirements of the body that results from excessive caloric intake and insufficient physical activity. However, an emerging paradigm is that immunity and metabolism are inextricably linked. Because energy is required to fight infection, starvation suppresses immune response. Inflammation and infection, in turn, favor catabolism and downregulate anabolic signals such as those triggered by insulin. This paradigm offers a new perspective, which suggests that pollutant exposure when superimposed on diabetes and obesity could further aggravate the energy mismatch by triggering immune responses and inducing inflammation. Hopefully, this perspective will lead to a better understanding of the role of modifiable environmental factors in the development of diabetes and obesity and may help in devising new strategies for preventing or managing these epidemics in the future.

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