Possible Role of Insulin on the Pathogenesis of Macrovascular Disease in Human Diabetics: Clinical Survey among 526 Japanese Diabetic Patients

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Clinical studies were carried out on 526 out-patients with diabetes mellitus on whom the progress of the disease could be followed up for more than 5 years (average 10.3 years). The results obtained were as follows: (1) Ischemic ECC abnormality was noted at a higher frequency in the obese group than in the non-obese group. Even when comparisons were made of the same condition based on the duration of the disease, age, cholesterol level and blood pressure, a similar tendency was observed. (2) Ischemic ECG abnormality was encountered more frequently in the obese group undergoing treatment with insulin or oral hypoglycemic agents, whereas in the non-obese group no difference existed from those undergoing diet treatment. (3) Ischemic ECG abnormality developed in 40.2% of the oral agents group, 40.0% of the insulin group and 9.1% of the diet group in the obese diabetics, while no difference was observed between therapeutic agents in the non-obese diabetics. It might be concluded that a specific state of being obese, or obesity coupled with a state assisting endogenous and exogenous hyperinsulinemia may contribute to the development of atherosclerosis in diabetics.

Atherosclerosis in diabetic patients tends to occur at an earlier age and with greater severity than in non-diabetic subjects. The evidence for this is derived from the reported clinical and autopsy data. However, the fact that clinically significant atherosclerotic lesions in diabetes appear to have little relationship to the duration or severity of the disease, and are not relieved by current therapeutic regimes, suggests that it is unlikely that hyperglycemia is the essential factor promoting atherosclerosis in diabetics. Hyperlipidemia, obesity, hypercoagulability, hypertension and an elevated lipid peroxide level all occur in diabetics but none of these can fully explain the association of diabetes with atherosclerosis.
Considerable controversy exists regarding the role of insulin, and Stout has shown evidence for the promoting influence of insulin in the development of atherosclerosis in experimental situations. Recent results from prospective studies of coronary heart disease in Helsinki, Paris, and Busselton, Australia have incriminated hyperinsulinemia as a risk factor in nondiabetic populations. The current clinical survey consequently has been undertaken to examine the possible role of insulin on the pathogenesis of macrovascular disease in human diabetic patients.

**Subjects and Methods**

The subjects comprised 526 outpatients with diabetes mellitus attending the Third Department of Internal Medicine, Nagoya University Hospital, for whom the progress of the disease could be followed up for more than 5 years (average 10.3 years). The subjects were divided into obese and non-obese groups, and the frequency of the vascular impairments was compared by further classifying them according to the method of treatment and the degree of diabetes.

**Results**

*Frequency of angiopathy in the obese and the non-obese diabetics*

Ischemic ECG abnormality and retinopathy were noted at a high frequency in the obese group (Fig. 1). The frequency of ECG abnormality was related to age and that of retinopathy to the duration of the disease. A comparison was then made of the same conditions for a duration of the disease of 11 to 15 years, at ages ranging from 41 to 60. No difference in the progress of retinopathy was observed between the obese and non-obese groups, while ischemic ECG changes were noted at a higher frequency in the obese group. A similar comparison was made among those showing normal cholesterol levels and normal blood pressure, and a similar tendency was observed. Comparison according to the degree of control of diabetes showed that ECG abnormality was observed at a high frequency in the obese group regardless of good or poor control. On the other hand, retinopathy showed no difference between the obese and non-obese groups.

![Fig. 1. Frequency of ECG abnormality and retinopathy.](image)
hand, retinopathy was observed in the patients with poor control among both the obese and non-obese groups.

**Relationship between method of treatment and angiopathy (Fig. 2)**

Ischemic ECG abnormality was encountered at a high frequency in the obese group undergoing treatment with oral hypoglycemic agents or insulin, whereas in the non-obese group no difference existed from those undergoing diet treatment. In both groups, retinopathy occurred at a higher frequency among those being treated with oral agents or insulin than those on diet treatment.

![Diagram](image1.png)

**Fig. 2. Frequency of ECG abnormality and retinopathy related to the method of treatment.**

**Frequency of newly diagnosed ischemic ECG abnormality (Fig. 3)**

When comparisons were made among those diabetics who hadn't had ischemic ECG abnormality at their initial visits, the results revealed that ischemic ECG abnormality developed in 40.2% of the oral hypoglycemic group, 40.0% of the insulin group and 9.1% of the diet group in the obese patients, while no difference
was observed between therapeutic agents in the non-obese diabetics.

**Discussion**

Porte and Bagdade\(^{10}\) already have shown that there is a linear relationship between relative body weight and basal insulin secretion. In diabetics the relationship between basal insulin and obesity is unaltered, although their response to an acute glucose challenge is impaired. Therefore obese diabetics have higher basal insulin levels and higher post-glucose values than non-obese diabetic patients\(^{3,5}\). Our current clinical survey might suggest that a specific state of being obese, or obesity coupled with a state assisting endogenous and exogenous hyperinsulinemia may contribute to the development of atherosclerosis in diabetics.

Insulin has been shown even in small concentration to stimulate arterial smooth muscle cell proliferation\(^{5,11}\), to enhance glucose incorporation into the aorta\(^{12}\) and labeled acetate incorporation into sterols in cultured rat arterial smooth muscle cells\(^{13}\), and to inhibit lipolysis in the arterial wall\(^{14}\). From this evidence Stout\(^{3,5}\) emphasized that insulin has an important role in the development of atherosclerosis either by a direct effect in the artery, or by way of its effect on lipid metabolism. Grant\(^{15}\) also reported that insulin might inhibit hydrolysis of cholesterol ester in the arterial smooth muscle cell, thus accelerating lipid deposition. Stout\(^{3,5}\) further pointed out the following possibilities. In insulin-treated diabetics, insulin levels are not related to meals or to blood sugar levels. Hence between meals and at night, insulin levels in diabetics are higher than in nondiabetics. Another difference between nondiabetics and diabetics is the route of insulin delivery into the circulation. Normally, insulin is secreted into the portal system and reaches the liver in high concentrations. The injected insulin first passes through the systemic circulation, instead of through the portal circulation and the liver as with normal insulin secretion.

If insulin has a role in the pathogenesis of atherosclerosis, measures to lower insulin levels might prevent the disease. These measures would include avoidance of obesity, regular physical exercise, and in addition, for insulin-dependent diabetics, the development of methods of delivering exogenous insulin in a way that is more physiological\(^{3,5}\).

On the other hand, Wolinsky et al.\(^{16}\) have shown evidence of reduced cholesterol acid hydrolase activity in alloxan-diabetic rats, with reversal of these changes by insulin administration. Therefore long-term prospective studies, taking into account all coronary risk factors and direct experimental evidence that hyperinsulinemia can enhance atherogenesis will be needed.

**References**

Pathogenesis of macrovascular disease


