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# Effect of insulin therapy on body fat distribution in NIDDM patients with secondary sulfonylurea failure: a preliminary report

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**Objective:** To clarify the influence of insulin therapy on body weight and fat distribution, we compared these parameters in five non-insulin dependent diabetes mellitus (NIDDM) patients, with secondary sulfonylurea failure, before and after insulin therapy. Body weight increased significantly after instituting insulin treatment. However, the visceral to subcutaneous fat (V/S) ratio decreased significantly due to a marked increase in S-fat without a change in V-fat. Insulin therapy necessitated by sulfonylurea failure does not appear to accelerate the atherogenic process in NIDDM patients as there is no increase in visceral fat.

## Introduction

Secondary sulfonylurea failure is common in patients with non-insulin dependent diabetes mellitus (NIDDM), the incidence rises with increasing disease duration (Bernhard, 1965) and inadequate glycemic control may necessitate insulin therapy aimed at preventing diabetic complications. Even NIDDM patients with adequate dietary control can gradually become unresponsive to oral hypoglycemic agents. Reportedly, 14.7% of NIDDM patients ultimately require insulin therapy due to secondary sulfonylurea failure (Evans *et al*, 1984).

Although most Caucasian NIDDM are insulin resistant and thus hyperinsulinemic, Japanese NIDDM generally show low insulin secretion and are therefore more likely to require insulin. Though insulin prevents microangiopathic complications, its effects on macroangiopathic complications such as heart disease and stroke remain controversial. Insulin may exacerbate hyperinsulinemia, especially in obese NIDDM, which is an independent risk factor for atherosclerosis.

Furthermore, the weight gain that results from insulin therapy may increase the macroangiopathic risk as obesity is a major risk factor for atherosclerosis. The type of fat which accumulates is also important as visceral, or abdominal, fat is reportedly associated with a higher incidence of heart disease than subcutaneous fat (Fujioka, 1987).

We thus questioned whether the benefits of improving glycemic control with insulin are outweighed by the health hazards of obesity. Body weights and fat distributions, determined by computerized tomograph (CT), were compared before and three to six months after starting insulin treatment in five NIDDM patients with secondary sulfonylurea failure.

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## Subjects, Methods and Results

The subjects were five NIDDM patients seen regularly at Keio University Hospital outpatient clinics. All gave fully informed consent. Investigations were performed in strict accordance with Declaration of the Helsinki principles.

CT scanning was performed at the umbilical leval, by the method of Tokunaga *et al*, to measure total (T-fat), visceral (V-fat) and subcutaneous (S-fat) fat areas (Groop *et al*, 1989). We then calculated the V-fat to S-fat, or V/S, ratio.

Determined body weight, body mass index (BMI), glycosylated hemoglobin (HbA1c%) and serum lipids (total cholesterol: TC, high density lipoprotein cholesterol: HDL-C: triglycerides: TG). HbA1c% was determined by high performance liquid chromotography (HCL-723 GHB-III, Toso, Japan), lipids by an enzymatic method.

All subjects underwent these examinations twice: prior to and 3–6 months after starting insulin therapy.

Results are presented as means $\pm$ s.d. The two-tailed paired *t*-test was used to compare metabolic characteristics before and after insulin therapy, the unpaired version to compare fat distributions. All calculations were performed using StatviewII (Abacus Concepts, Inc, Berkeley, CA, USA) on a Macintosh Quadra 650 (Apple Japan Inc, Tokyo, Japan). A value of $P < 0.05$ was considered statistically significant.

The clinical characteristics of the five patients are shown in Table 1. These subjects experienced significant increases in BMI and body weight after three to six months of insulin treatment. HbA1c levels decreased significantly, reflecting improved glycemic control. There were no statistically significant changes in TC, HDL-C or TG. After insulin treatment, V-fat areas did not change, but S-fat increased significantly, resulting in a significant increase in T-fat and a decrease in the V/S ratio.

**Table 1** The clinical characteristics of the five patients with secondary sulfonylurea failure who were examined pre- and post-insulin therapy

| | *Pre-insulin* | *Post-insulin* |
|---|---|---|
| Body Weight (kg) | 49.8 ± 5.9 | 53.3 ± 6.7** |
| BMI | 20.5 ± 0.4 | 22.0 ± 0.3** |
| HbA1c (%) | 9.5 ± 1.1 | 8.8 ± 1.1* |
| TC (mg/dl) | 203 ± 44.6 | 197 ± 40.2 |
| HDL-C (mg/dl) | 47.3 ± 11.2 | 44.0 ± 8.4 |
| TG (mg/dl) | 136 ± 33.6 | 146.5 ± 53.7 |
| T-fat | 177.6 ± 46.9 | 213.2 ± 46.4* |
| V-fat | 86.5 ± 15.4 | 81.2 ± 13.2 |
| S-fat | 91.1 ± 36.1 | 131.9 ± 41.1* |
| V/S | 1.07 ± 0.39 | 0.66 ± 0.21* |

*$P < 0.05$,
**$P < 0.01$.

## Discussion

Appropriate timing of the transition from sulfonylurea to insulin is a clinical challenge in NIDDM. The weight gain associated with insulin is distressing for patients and, in Caucasian populations, has been associated with progression of atherosclerosis (Hanpt *et al*, 1977). We examined changes in body weight, fat distribution and several risk factors for macroangiopathy in insulin-treated patients with secondary sulfonylurea failure.

Our patients showed improvements in HbA1c and a decreased V/S ratio, possibly reflecting improved glucose metabolism. Visceral fat accumulation is widely recognized as being associated with metabolic disturbances and atherosclerosis. Obesity is a well known health risk. We found that insulin treatment increased body weight and increased S-fat which led to an increase in T-fat and a decrease in the V/S ratio without affecting V-fat and serum lipids. Our results suggest that insulin treatment in NIDDM patients with secondary sulfonylurea failure does not accelerate the atherosclerotic process, despite a slight increase in body weight. Although we could not evaluate serum insulin levels in these patients, it appears that insulin does not accelerate the atherogenic process in Japanese NIDDM. Numerous studies have documented the health hazards associated with excess visceral fat (Hubert *et al*, 1983; Larsson *et al*, 1984; Tokunaga *et al*, 1983).

In the diabetic patient, cardiovascular risks are of particular concern. The findings obtained in this preliminary study may allay the concerns of those experiencing insulin-induced weight gain. Given the discrepancy between our results and those in Caucasisn populations, further study is needed to determine whether these findings are applicable only to Japanese (and possibly other Asian) NIDDM patients. We speculate that the insulin deficiency seen in Japanese NIDDM, in contrast to the hyperinsulinemia of European NIDDM, may account for this difference.

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