

INSULIN THERAPY INDUCED ADIPOSITY EVALUATED BY COMPUTED TOMOGRAPHY IS NOT VISCERAL

Ahmed Elsayed¹, Soliman ElGebely², Ahmed Galal³

ABSTRACT

Objective: In individuals with type 2 diabetes, weight gain during treatment with insulin and other agents prevents the attainment of glycemic targets and probably limits the success of treatment. Studies have attempted to elucidate the mechanisms behind the apparent paradox of insulin improving glycemic control and cardiovascular risks, while causing weight gain. The aim of this study is to clarify the influence of insulin therapy on body weight and differential fat distribution (visceral or peripheral) in newly insulin treated type 2 diabetic male patients.

Patients and Methods: The study was conducted on 26 type 2 diabetic male patients evaluated at baseline and 12 months after instituting insulin therapy. Body mass index (BMI), absolute waist circumference (AWC), systolic and diastolic blood pressure, HbA1c% were estimated. Abdominal Computed tomography was applied to evaluate areas of subcutaneous fat (SF) and visceral fat (VF) before and after insulin therapy.

Results: There is significant reduction in HbA1c (9.03 ± 0.72 vs. 7.50 ± 0.58 , $p < 0.001$) and significant increase body mass index (BMI = 28.92 ± 1.39 vs. 29.81 ± 1.27 , $p = 0.02$). However there was non significant changes in the AWC 103.27 ± 3.87 Vs 105.14 ± 3.25 , $P = 0.065$, VF 121.01 ± 5.84 Vs 123.01 ± 5.55 , $p = 0.213$, SF 206.54 ± 9.93 Vs 212.12 ± 11.62 , $P = 0.069$ and V/S ratio 0.59 ± 0.03 vs. 0.58 ± 0.03 , $P = 0.365$.

Conclusion: Weight gain in the newly insulin treated type 2 diabetic patients during 12 months duration is equally distributed in both peripheral and visceral fat. So, insulin therapy does not appear to increase the visceral fat in type 2 diabetic patients which is strongly linked to atherosclerosis. Longer-term follow up and bigger sample size are necessary to address the issue of the kinetics of weight gain and to establish the possible correlation with other cardiovascular risk markers.

KEYWORDS: Insulin therapy, Type 2 diabetes, Adiposity, Visceral fat, Fat distribution, Computed tomography.

Pak J Med Sci April 2007 Vol. 23 No. 2 161-166

INTRODUCTION

In patients with diabetes, the benefits of tight glycemic control are unequivocal, delayed onset and progression of complications such as retinopathy, nephropathy, and neuropathy. Unfortunately intensive insulin therapy and some oral antidiabetic agents come at the price of weight gain, a condition that can prevent attainment of tight glycemic goals and probably limits success of treatment.¹

Weight gain is observed when insulin is introduced after oral agents have failed, but also when insulin is introduced shortly after the diagnosis of diabetes. The mechanisms of this weight gain are incompletely understood, but reduction of energy lost by glucosuria and

1. Dr. Ahmed Elsayed, MD
Specialist Endocrinologist
Endocrinology Unit,
Al-Amiri Hospital,
Kuwait.
2. Dr. Soliman ElGebely, MD
Specialist Diabetologist,
Diabetes Unit, Mubarak Al-Kabeer Hospital,
Kuwait.
3. Dr. Ahmed Galal, MD
Prof. of Radiology,
Mansoura University,
Egypt

Correspondence

Dr Ahmed Elsayed,
E-mail: ahmedemam6@hotmail.com

- * Received for Publication: June 27, 2006
- * Revision Received: July 17, 2006
- * Revision Accepted: January 3, 2007

reduction of energy needed for glucose production, anabolic effects of insulin, appetite increase through hypoglycemia, are the main determinants.² In the UKPDS, at 10 years of the study, patients treated with insulin gained 2kg more, i.e. 2.5% of the average weight of patients included in the trial, than patients treated with sulfonylurea. The reasons of the excess of weight gain with insulin as compared with sulfonylurea remain unclear. Patients with type 2 diabetes treated with insulin gain weight only during the first 2-3 years after insulin introduction. The weight stabilizes thereafter. Type 2 diabetes usually remains unknown for years before diagnosis and patients may lose weight during this long period of time preceding diagnosis. It is hypothesized that the weight gain observed after the introduction of insulin may simply correspond to the reexpression of the physiologically controlled body weight.³

However, obesity is a heterogeneous disorder in that the storage depot for excess calories differs widely between individuals, and these differences in fat distribution confer differential health risks. An excess of fat in the abdominal region is a better predictor of coronary heart disease (CHD), as well as their risk factors (dyslipidemia, glucose intolerance, and hyperinsulinemia), than the total amount of adipose tissue.⁴⁻⁷

Most studies designed to assess the health risks of body fat distribution have used anthropometric measures such as waist circumference or waist-to-hip ratio (WHR) to estimate the amount of abdominal adipose tissue. Both of these measures are known independent predictors of metabolic risk factors for CHD in men and women, and it is likely that this association is due to an enlargement of visceral fat stores. In fact, the associations between risk factors and visceral adipose tissue (VAT), measured directly with computed tomography (CT) or magnetic imaging resonance, are stronger than the associations observed with WHR or waist circumference.⁸⁻¹² In addition, visceral fat accumulation also contributes to CHD risk factors in healthy, nonobese individuals.^{10,13-15}

Thus, the amount of VAT may be the best predictor of obesity-related metabolic complications and could be more clinically relevant than the quantity of total body fat for assessment of risk status.

The aim of this study is to clarify the influence of insulin therapy on body weight and differential fat distribution (visceral or peripheral) in newly insulin treated type 2 diabetic patients.

PATIENTS AND METHODS

This study was conducted in Amiri and Mubarak Al kabeer hospitals, Kuwait on 26 Type 2 diabetic male patients. The evaluation was carried out before and after 12 months of their insulin therapy. The body weight of patients was stable over the preceding 6 months, being within ± 1 kg. The patients were treated with two or three injections of insulin per day (1.2 ± 0.3 U/Kg/day) to obtain glycaemic and HbA1c levels close to those recommended (less than 7%). Exclusion criteria included Drugs known to increase body weight or affect fat distribution especially thiazolidindiones (TZDs) and steroids or any condition leading to water and salt retention (heart failure, liver failure or severe kidney failure). All patients were advised by a physician and a dietitian regarding their diet and physical activity. All patients were fully informed of the purpose of the study and gave informed voluntary consent according to the protocol approved by the local ethics committee and in accordance with the ethical standards laid down in the Helsinki declaration.

Each patient was studied at a single consultation, on two separate occasions under identical conditions and separated by 12-months. Each evaluation comprised of a full clinical examination (weight, height, body mass index, absolute waist circumference), biochemical measurements (Blood glycated hemoglobin, urea, creatinine).

Height, weight and body mass index (BMI): Standing height and weight were measured with the subjects in light clothing and without shoes. Height was recorded to the nearest

centimeters and weight to the nearest 0.1 kg. The weighing scales (Detecto-Medic, New York, USA) were standardized daily using standard weights of 20 and 70 kg. BMI, defined as weight in kilograms per height (in meters) squared was calculated and used as an index for obesity.

Blood glycated hemoglobin (HbA1c): was measured on a DCA 2000 analyzer with dedicated reagent cartridges supplied by Bayer Corporation (Elkhart, IN, USA).

Computed tomography (CT) was applied to evaluate areas of subcutaneous (SF) and Visceral fat (VF) before and after insulin therapy. The CT scan was performed at the umbilical level with the subject resting in the supine position. The total area of the cross sectional-fat region (i.e., including both SC and VF) at the umbilical level was traced inside the skin to calculate the total number of pixel showing CT values between - 50 and -150 Hounsfield units. These respective areas (centimeters squared) were measured by tracing object contours on the films of each individual scan using the computerized planimetric method. The subcutaneous fat was clearly defined between the skin and muscles, the visceral fat area was traced manually along the inside of the abdominal wall, and the number of pixels showing the same range of CT values was calculated for this region.

The ratio of the visceral to subcutaneous fat was calculated as follows (visceral fat area)/(total fat area -visceral fat area) ×100(%).

Statistical analysis: The data are presented as mean ± SD. Independent sample t-test was used to compare clinical, biochemical, and fat distribution before and after insulin therapy. The statistical analysis was carried out using the SPSS 12 for windows.

Table-I: Clinical characteristics of study population

No.	26
Age (years)	50.23±4.23
Sex	male
BMI(kg/m ²)	28.92±1.39
Duration of diabetes (years)	7.23±1.61
Insulin dose (U/Kg / Day)	1.2±0.3 U/Kg/day

RESULTS

Table-I summarizes the clinical characteristics of the study population at baseline before instituting insulin therapy. All patients were males to eliminate the sex differences in the propensity to store fat in the abdominal region, Mean age 50.23±4.23 years, BMI 28.92±1.39kg/m², duration of diabetes 7.23±1.61 years and the average daily insulin dose was 1.2±0.3 U/Kg/day.

Table-II showed significant reduction in HbA1c (9.03±0.72 vs. 7.50±0.58, p<0.001) (fig-1) and significant increase body mass index (BMI =28.92±1.39 vs 29.81±1.27, p=0.02) (fig-1). However there was non significant changes in the AWC 103.27±3.87 Vs 105.14±3.25, P=0.065, VF 121.01±5.84 Vs 123.01±5.55, p=0.213, SF 206.54±9.93 Vs 212.12±11.62, P = 0.069 (fig-2) and V/S ratio 0.59±0.03 vs. 0.58±0.03, P=0.365.

DISCUSSION

In the present study, body weight increased significantly one year after instituting insulin treatment. However, there are non significant changes in SF, VF and V/S ratio measured by abdominal CT before and after insulin therapy. So, insulin therapy does not appear to increase the visceral fat in type 2 diabetic patients which is strongly liked to atherosclerosis.

Treatment of diabetes mellitus with medications, including insulin, often leads to weight gain through a variety of mechanisms.^{16,17}

Table-II: Mean changes of BMI, AWC, BP, HbA1c, VF, SF and V/S ratio

	Pre insulin therapy	post insulin therapy	P Value
BMI(kg/m ²)	28.92±1.39	29.81±1.27	0.02*
AWC(cm)	103.27±3.87	105.14±3.25	0.065
SBP	125.81±8.53	125±8.33	0.731
DBP	76.88±5.89	77.65±5.56	0.630
HbA1c (%)	9.03±0.72	7.50±0.58	<0.001**
VF(cm ²)	121.01±5.84	123.01±5.55	0.213
SF(cm ²)	206.54±9.93	212.12±11.62	0.069
V/S	0.59±0.03	0.58±0.03	0.365

* Significant. ** Highly significant BMI: Body mass index
AWC: Absolute waist circumference SBP&DBP: Systolic & Diastolic blood pressure HbA1c: glycated hemoglobin
VF&SF: visceral & Subcutaneous fat
V/S: visceral/Subcutaneous ratio

Weight gain can have adverse consequences for patients with type 2 diabetes, many of whom are overweight or obese, because obesity is linked to insulin resistance syndrome and its related medical consequences. It has been suggested that insulin-induced weight gain may increase absolute cardiovascular risk, although this issue has not yet been resolved. Most studies investigating body composition changes suggested that this weight gain is made of fat.¹⁶ 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 type 2 diabetics, which is an independent risk factor for atherosclerosis.¹⁸

Insulin-induced body composition changes have been particularly well studied in Type 1 diabetic patients. In this population group, the weight gain is predominantly composed of fat-free mass.¹⁹ When optimal glycaemic control is achieved, the fat-free mass of Type 1 diabetic patients is significantly greater than that of non-diabetic control subjects. However, in Type 2 diabetic patients the question addressing body composition and differential fat distribution is not fully answered. There are well-known and physically obvious sex differences in the propensity to store fat in the abdominal region. On average, men have twice as much visceral fat as premenopausal women when matched for total body fat.^{20,21}

Our study showed the benefit of one-year insulin therapy in type 2 diabetic male patients on glycemic control with significant reduction in HbA1c. Although this improvement in glycemic control was at the expense of the significant increase in body mass index, there was non significant changes in the AWC, VF, SF and V/S ratio (Table-II). Weight gain in our insulin treated diabetic patients could be explained by the anabolic effect on both adipose and muscles together with the antinaturetic effect of the insulin that leads to water and sodium retention.^{22,23}

This in agreement with another 6-month study in patients with type 2 diabetes showed that a weight gain of 3.2kg with intensive therapy ($n = 43$) was approximately equally distributed between lean and fat mass, and the fat was proportionately distributed to central and peripheral regions.²⁴ In other study of type 2 diabetics showed that 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.²⁵

On the other hand, Sinha et al. reported a study of 15 individuals with type 2 diabetes who gained 4kg, mostly as truncal fat, when treated with insulin for 6 months.¹⁶ If this is the case, the predominant increase in abdominal fat mass may partially offset the overall benefit of insulin in glycemic control and the prevention of cardiovascular complications,

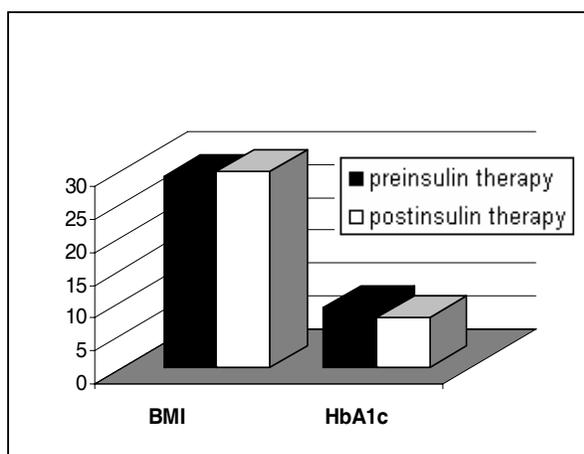


Fig-1: Comparison of BMI and HbA1c pre and postinsulin therapy

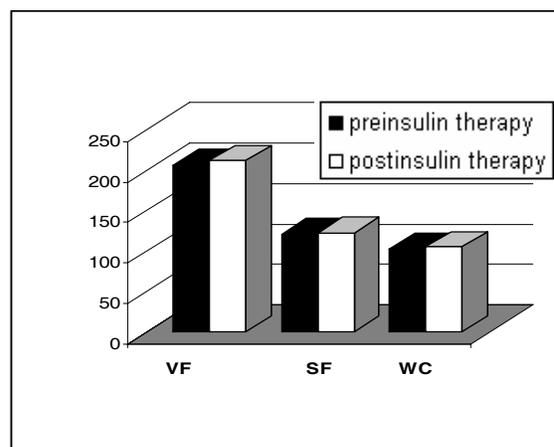


Fig-2: Comparison of VF, SF and WC pre and postinsulin therapy

and the distribution of added weight may be relevant to insulin resistance and cardiovascular risk.

Other studies showed the adverse effect of insulin therapy on blood pressure and lipids. Yki-Jarvinen et al, reported that weight gain at 12 months in patients with insulin-treated type 2 diabetes was associated with increments in blood pressure and LDL-cholesterol, changes that could potentially increase cardiovascular risk.²⁶ For type 1 diabetes, Purnell et al. reported that patients who gained excessive weight following intensive insulin therapy were likely to experience an increase in blood pressure and changes in lipid levels similar to those observed in the insulin resistance syndrome, a condition recognized to increase the risk for coronary heart disease over time.²⁷

Multiple strategies can be used for weight control in patients with type 2 diabetes, but many current approaches have shortcomings. A metformin/insulin combination therapy is a useful approach which limits weight gain. New insulin analogs may offer comparable benefits, but further study is needed to define these with precision.

CONCLUSION

The present study showed that weight gain in the newly insulin treated Type 2 diabetic patients during 12 months duration is equally distributed in both peripheral and visceral fat, therefore reducing the fear of gaining weight on cardiovascular risk, especially in light of the improvement brought about by a decreased HbA1c., suggesting that patients with the greatest improvement in metabolic control should also be those who require the most aggressive nutritional advice. Longer-term follow up and bigger sample size are necessary to address the issue of the kinetics of weight gain and to establish the possible correlation with other cardiovascular risk markers.

REFERENCES

- Heller S. Weight gain during insulin therapy in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2004;65 Suppl 1:S23-7.
- Larger E, Rufat P, Dubois-Laforgue D, Ledoux S. Insulin and weight gain: myth or reality? *Diabetes Metab* 2001;27:S23-7.
- Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352(9131):837-53.
- Despres JP, Lemieux I, Prud'homme D. Treatment of obesity: need to focus on high risk abdominally obese patients. *BMJ* 2001;322:716-20.
- Fujimoto WY, Bergstrom RW, Boyko EJ, Chen KW, Leonetti DL, Newell-Morris L, et al. Visceral adiposity and incident coronary heart disease in Japanese-American men: the 10-year follow-up results of the Seattle Japanese-American Community Diabetes Study. *Diabetes Care* 1999;22:1808-12.
- Rexrode K, Carey V, Hennekens C, Walters E, Colditz G, Stampfer M, et al. Abdominal adiposity and coronary heart disease in women. *JAMA* 1998;280:1843-48.
- Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjostrom L. Distribution of adipose tissue and risk of cardiovascular disease and death: A 12 year follow up of participants in the population study of women in Gothenburg, Sweden. *Br Med J (Clin Res Ed)* 1984;289:1257-61.
- Lemieux S: Contribution of visceral obesity to the insulin resistance syndrome. *Can J Appl Physiol* 2001;26:273-90.
- Brochu M, Starling RD, Tchernof A, Matthews DE, Garcia-Rubi E, Poehlman ET. Visceral adipose tissue is an independent correlate of glucose disposal in older obese postmenopausal women. *J Clin Endocrinol Metab* 2000;85:2378-84.
- Carey D, Jenkins A, Campbell L, Freund J, Chisholm D. Abdominal fat and insulin resistance in normal and overweight women—direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. *Diabetes* 1996;45:633-8.
- Ross R, Fortier L, Hudson R. Separate associations between visceral and subcutaneous adipose tissue distribution, insulin and glucose levels in obese women. *Diabetes Care* 1996;19:1404-11.
- Despres J, Nadeau A, Tremblay A, Ferland M, Moorjani S, Lupien P, et al. Role of deep abdominal fat in the association between regional adipose tissue distribution and glucose tolerance in obese women. *Diabetes* 1989;38:304-9.
- DeNino WF, Tchernof A, Dionne II, Toth MJ, Ades PA, Sites CK, et al. Contribution of abdominal adiposity to age-related differences in insulin sensitivity and plasma lipids in healthy nonobese women. *Diabetes Care* 2001;24:925-32.
- DiPietro L, Katz L, Nadel E. Excess abdominal adiposity remains correlated with altered lipid concentrations in healthy older women. *Int J Obes Relat Metab Disord* 1999;23(4):432-6.

15. Park KS, Rhee BD, Lee KU, Kim SY, Lee HK, Koh CS, et al. Intra-abdominal fat is associated with decreased insulin sensitivity in healthy young men. *Metabolism* 1991;(6):40:600-3.
16. Sinha A, Formica C, Tsalamandris C, Panagiotopoulos S, Hendrich E, DeLuise M, et al. Effects of insulin on body composition in patients with insulin-dependent and non-insulin-dependent diabetes. *Diabet Med* 1996;13: 40-6.
17. Mäkimattila S, Nikkilä K, Yki-Järvinen H. Causes of weight gain during insulin therapy with and without metformin in patients with Type II diabetes mellitus. *Diabetologia* 1999;42(4):406-12.
18. Bonora E. The metabolic syndrome and cardiovascular disease. *Ann Med* 2006;38(1):64-80.
19. The Diabetes Control and Complications Trial Research Group. Influence of intensive diabetes treatment on body weight and composition of adults with type 1 diabetes in the Diabetes Control and Complications Trial. *Diabetes Care* 2001;24:1711-21.
20. Enzi G, Gasparo M, Biondetti P, Fiore D, Semisa M, Zurlo F. Subcutaneous and visceral fat distribution according to sex, age and overweight, evaluated by computed tomography. *Am J Clin Nutr* 1986;44(6):739-46 .
21. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Despres J. Sex differences in the relation of visceral adipose tissue accumulation to total body fatness. *Am J Clin Nutr* 1993;58(4):463-67.
22. Ter Maaten JC, Serne EH, Van Eps WS, Ter Wee PM, Donker AJ, Gans RO. Effects of insulin and atrial natriuretic peptide on renal tubular sodium handling in sickle cell disease. *Am J Physiol Renal Physiol* 2000;278(3):F499-505.
23. Ter Maaten JC, Bakker SJ, Serne EH, ter Wee PM, Donker AJ, Gans RO. Insulin's acute effects on glomerular filtration rate correlate with insulin sensitivity whereas insulin's acute effects on proximal tubular sodium reabsorption correlation with salt sensitivity in normal subjects. *Nephrol Dial Transplant* 1999;14(10):2357-63.
24. Bagg W, Plank LD, Gamble G, Drury PL, Sharpe N, Braatvedt GD. The effects of intensive glycaemic control on body composition in patients with type 2 diabetes. *Diabetes Obes Metab* 2001;3(6):410-16.
25. Takei I, Takayama S, Yamauchi A, Nakamoto S, Kitamura Y, Katsukawa F, et al. Effect of insulin therapy on body fat distribution in NIDDM patients with secondary sulfonylurea failure: a preliminary report. *Eur J Clin Nutr* 1998;52(2):153-4.
26. Yki-Jarvinen H, Ryysy L, Kauppila M, Kujansuu E, Lahti J, Marjanen T, et al. Effect of obesity on the response to insulin therapy in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1997;82(12):4037-43.
27. Purnell JQ, Hokanson JE, Marcovina SM, Steffes MW, Cleary PA, Brunzell JD. Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: results from the DCCT. *Diabetes Control and Complications Trial. JAMA* 1998;280(2):140-6.