FROM OBESITY TO DIABETES

(Obeziteden Diyabete)

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Summary

Obesity is an important factor in develpoments of IGT and Diabetes. This effect of obesity is realised through fat tissue as an endocrine organ. Adipose hormones are Leptin, Adiponectin, Resistin and TNF-α. These adipose hormones play an important role on insulin resistance and insulin resistance is practically the first step in developing Type 2 Diabetes.

Recent studies show that weight reduction can prevent IGT even Type 2 Diabetes.

Key words: Obesity, diabetes

Özet

Obezite sırasıyla IGT, Tip 2 Diabet gelişmesinde en önemli faktördür. Obezitenin bu etkilerinde en önemli rolü bir endokrin organ olarak yağ dokusu oynar. Yağ dokunun endokrin aktivitesi, Leptin, Resistin, Adiponektin ve TNF-α gibi salgıladığı hormonlar üzerinden olmaktadır. IGT ve Diabet gelişmesinde ilk adım insülin rezistansı olmaktadır ve yağ doku hormonlarının insülin direnci gelişimi üzerinde belirleyici etkiler bulunmaktadır.

Güncel olarak yapılan çalışmalar yalnızca kilo vermenin IGT ve hatta Diabeti dahi önleyebileceğini göstermektedir.

Anahtar kelimeler: *Obezite, diabet*

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OBESITY in WORLD and OUR COUNTRY

Nowadays obesity is a serious health problem in our country and also in the whole world. This problem is getting bigger and bigger like a rolling snowball, becoming a serious health problem for individuals as well as for society [1,2]. Obesity both in adults and children has become frightingly frequent. National Health and Nutrition Study in USA (NHANES I,II,III) has shown the increasing frequency of obesity from 1980 to 2000 like some plague. In this study, we can see that, from 1980 to 2000, obesity (individuals with BMI > 35) prevalance in adults has increased from 25% to 60%. In children such an incrase was also found, namely, from 13.6% to 24%. These values are by African-Americans and by individuals with Latin heritage are even 10% higher. If this trend of increase in the prevalance of obesity continues, in the year 2025 the obese population in America could be 100%.

In fact, the saturated and unsaturated fat ratio in diets of American individuals is getting lower. Between the years 1970 to 1990 the fat ratio in diet was 37%, this ratio is decreased to 26% between years 1990 to 2000. Such a paradox can be explained through increased food intake, a laid-back social life style, decreased physical activity in modern life style and an increase carbonhydrate intake from 40% to 54% [3-7].

In our country, we too go through similiar problems. The plague like increase of the prevalance of obesity can also be observed in our country. Data from Turkish Diabetes Etiology Study (TURDEP), made by WHO, Turkish Ministry of Health and University of Istanbul, data from several locally smaller studies and data from TEKHARF study made by Turkish Cardiology Society, show that the number of individuals with a BMI > 30 is suprisingly high. This prevalance in various studies differs from 22% to 31%. This trend of increasing prevalance of obesity leads to the assumption that by the year 2025 obese population would be around 40% in Turkey [8.9].

Prevalance of obesity shows similiar increases in all around the world. According to WHO-MONICA study, examaining data from 1980, the prevalance of obesity has increased in 2000 by following percentages in various continents: 210% in Northern America, 203% in Southern America, 221% in Europe, 235% in Asia, 187% in Africa and 205% in Oceania. All these data show the severity of the increase in obesity [10].

DIABETES in WORLD and OUR COUNTRY

In studies in U.S.A. it is observed that there is a correlation between the increase of obesity and the frequency of Type 2 Diabetes Mellitus. Especially in certain races (African - Americans, individuals with Latin heritage, Mexicans and Indians) this correlation even more significant. In these races the frequency of Diabetes in adults and children twice as high as the rest of population. In 1980 in America the prevalance of Diabetes was 4.4%, with 14.200.000 individuals. In 2002, paralel to the increasing prevalance of obesity, the prevalance of Diabetes has become 7.1% with 20.3 million individuals. The increase in Diabetes has been 23% in the last 20 years and the number of individuals with Diabetes has increased 5.5 millions [7].

Although not as high as the increase in the prevalance of Diabetes, the prevalances of Cardiovascular diseases, Hypertension, Stroke, Impaired Glucose Tolerance (IGT) causing macr- and microvascular complications have also increased. This means that in year 2000 36 million people in U.S.A. are living under the threat of cardiovascular diseases which are caused by or made susceptible to by Diabetes. (data from WHO-MONICA, NHANNES I,II,III studies) [10].

Table 1. Ratio of Obesity in World 1980 - 2000 (BMI > 30 kg/m^2) WHO - MONICA study Diabetes Care, 26:118, 2003

In other countries increase in Diabetes in correlation with the increase in obesity is also observed. In Europe, number of individuals with Diabetes has increased from 26.5 millions in 1980 to 39.9 millions in 2000, an increase by 24%. In Asia number of diabetics has increased from 85 millions to 133 millions in 2000, an increase of 57%. Also in Africa number of individuals has increased from 9.4 to 15 millions, an increase of 56% and in Oceania this number has increased from 1 million to 1.4 millions, increasing 35%.

In our country, observing the data from TEKHARF, TURDEP, reports from the Ministry of Health and various local studies, similiar outcomes can be seen. In 1980, 1.7 million diabetic patients, 4% of population has increased to 4.6 million, 7% of the population in 2000. This equals to an scary increase of 270%. This rather high increase can be explained through high birth ratio, rapid grow of industry and improvement in life style, changes in diet and physical surrondings and also the ability to obtain more reliable statistical data. In our country also, the increase of obesity seems to be causing a similiar increase of Diabetes [8,9].

In our country 9 million people have become prone to cardivascular diseases, stroke and other organ dysfunctions because of obesity, Diabetes and alike syndroms.

OBESITY and DIABETES

The journey from normal glucose tolerance to Diabetes goes through impaired fasting glucose (IFG) and then impaired glucose tolerance (IGT). IGT is more common in obese individuals and 70 % of individuals with IGT develop Diabetes in 20 years. In individuals with BMI > 30, the risk is 95%.

Obesity is without a question the most important cause leading to IGT and Diabetes. Genetic susceptibilty, diet, life style, ethnic factors also play an important role. Obesity's lead to Diabetes is more significant in young people and children rather then in adults, because obesity exposes genetic susceptibility to Diabetes [11].

Eventhough the exact mechanisms of development of Diabetes in obesity are still disputed, one can assume the main factor is insulin resistance. Factors leading to insulin resistance trigger

obesity and Diabetes in similiar ways. Insulin resistance is frequently observed in obese people and individuals with Type 2 Diabetes. IGT and Type 2 Diabetes have a tight correlation between visceral and central fat mass, which is caused by factors leading to insulin resistance. HOMA-IR (Homeostasis model for insulin resistance), fasting and after meal proinsulin ratio, 2 hours insulin level are methods for determining insulin resistance which support the correlation between Type 2 Diabetes, obesity and insulin resistance [11,12].

Table 2. A Look at The Epidemy of Diabetes in World

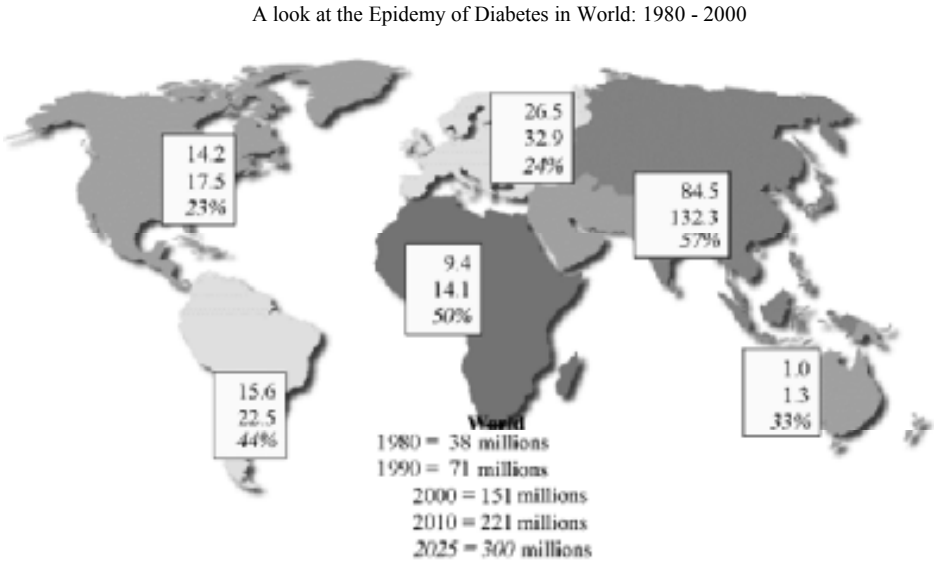


Table 3. Obesity and Type 2 Diabetes

Obesity:

- The most significant cause of Type 2 Diabetes
- The easy to change factor of Type 2 Diabetes

  In obesity incidence of Type 2 Diabetes increases
- Increase in BMI and Diabetes incidence are correlated
- Central / visceral fat mass ratio is reversed proportioned to Diabetes
- Weight loss improves blood glucose levels

  5-10 % weight loss decreases Diabetes incidence
- Obesity in Diabetics can be caused by insulin or sulphanylureas
- Weight loss decreases the need for insulin and / or oral antidiabetics in Type 2 Diabetics

Diabetes, 51 : 1505, 2002

Int. Jour. Obesity. 26(4):11,2002

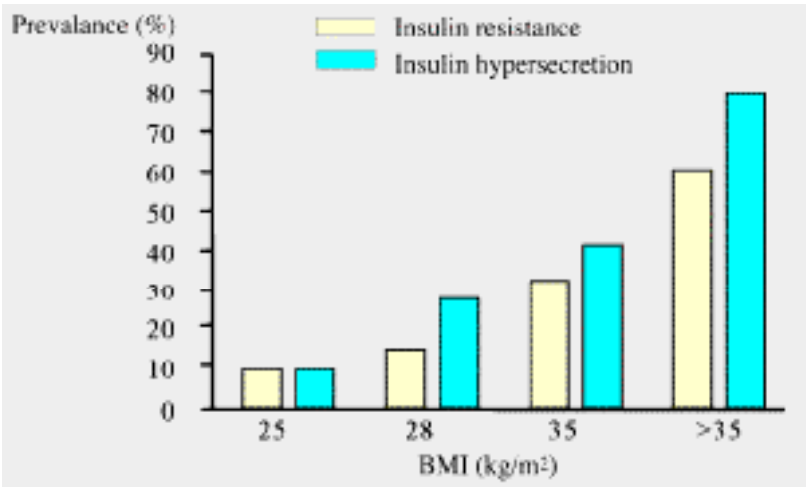
Int. Jour. Obesity. 26(2):18, 2003

It is easy to answer the question, how does obesity make an individual Diabetic?

In obese population insulin resistance is encountered 80%. Insulin resistance leads to hyperinsulinemia. To regulate the same amount of blood glucose, two or three times more insuiln is required (compansatuar hyperinsulinemia). A pancreas secreting immense amounts of insulin for years wears out resulting in decrease of insulin secreting capacity which results in IGT and later on in Type 2 Diabetes. Various other hormones and precursors also play different roles in this mechanism.

The relation between insulin resistance and Diabetes can be seen in Tables 4 and 5.

Table 4. The prevalance of insulin resistance is correlated with BMI



Ferrannini E, et al. J Clin Invest 1997; 100: 1166-73

Table 5. High visceral fat tissue increases insulin resistance and the risk for Diabetes

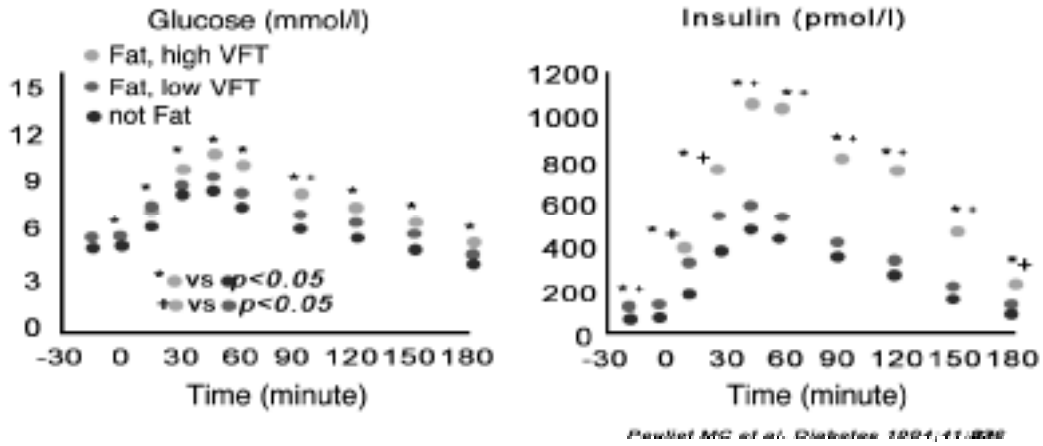
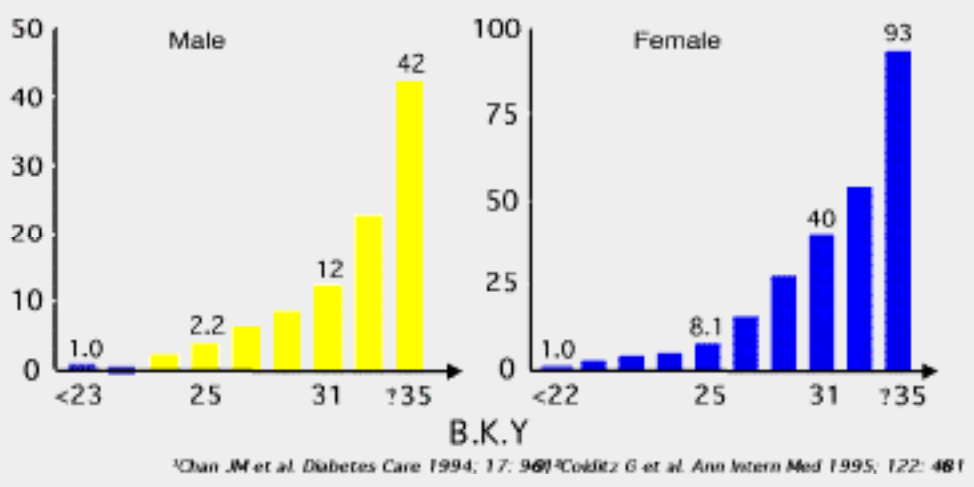


Table 6. Obesity is the primer risk factor for Type 2 Diabetes

Correction of Type 2 Diabetes risk for Ages



RELATION BETWEEN OBESITY and TYPE 2 DIABETES

1- Obesity is the most significant factor for Diabetes

2- Obesity is the easiest factor in Diabetes to intervene. If obesity can be prevented, so can be Diabetes.

3- Increase in BMI, waist - hip ratio and waist circumference are related to the incidence of Diabetes.

4- High central / visceral obesity ratio increases the risk for Diabetes.

5- Weight loss decreases the risk of Diabetes.

6- In obese population a weight loss of 5-10%, decreases the incidence of Diabetes 2 - 3 times.

7- In Type 2 Diabetic population the frequency of obesity is 80%. Weight loss in this population improves the blood glucose levels and reduces the risk of IGT developing to Diabetes.

RELATIONSHIP BETWEEN FAT TISSUE, INSULIN RESISTANCE AND DEVELOPMENT of DIABETES

Fat tissue, especially visceral fat tissue (fat tissue around omentum and inner organs) and subcutaneous fat tissue are called white fat tissue. Fat tissue around hip and gluteal region is more stabil and called the brown fat tissue.

White fat tissue is active, vital and affected by fat acides, triglycerids, LDL, various enzymes, hormones and insulin. This fat tissue is very much like placenta and hypophysis, secreting several hormones, hormon precursors and enzymes.

PRODUCTS of WHITE FAT TISSUE

1- Adiponectine (Exon 2)
2- Leptin
3- Resistan
4- HSD I-II (Hydroxy steroid dehidrogenase)
5- Cortisol
6- TNF-α
7- IL-6
8- AT, AT-2
9- Adiposine
10- PPAR-γ (Peroksizome proliferator receptor activator)
11- Gherlin
12- Phospholipids, fat ascides, triglycerids
13- Polypeptids, Adipsine and Antileptin

All these products can increase insulin resistance alone or together and cause development of Diabetes.

LEPTIN

Leptin is secreted from fat tissue and pancreas. It affects Hypothalamo-hypophysis-adrenal axis both central and peripheral. Leptin interacts with cortisol, ACTH, and Adrenal hormones. In obese individuals high levels of cortisol, glucagon and adrenal hormones increase both the leptin levels and leptin resistance. This leads to insulin resistance. Leptin levels are observed to be parallel to insulin levels and in case of leptin resistance fluctuations of glucose and insulin are seen (13).

Leptin is derived from fat tissue and pancreas and affects Hypothalamus through neuropeptid Y and melenocortin-D, causing,

1- Increase of sympatic activity, loss of energy through heat
2- Reducing hunger
3- Reducing insulin resistance, at the end effect weight loss.

In Leptin resistance, insulin resistance develops.

This is followed by,

1- Increase of triglycerids and fat ascides in organs and blood.
2- Increase of blood cortisone.
3- Reduced fat activity, increase in fat mass.
4- Dropped body heat, reduced sympatic activity, hesitated weight loss.
5- Reduced PPAR-γ and Adiponectine activity and increased levels of TNF-α, IL-6, PAI-I (insulin resistance).

RESISTIN

Fat tissue (especially white fat tissue), secretes resistin in accordance to fat mass.In table 7, effects of resistin and factors leading to insulin resistance are seen.

Table 7. Products of visceral fat tissue and insulin resistance

PRODUCTS of VISCERAL FAT TISSUE and INSULIN RESISTANCE

RESISTIN : Secreted from white fat tissue adipocytes in accordance to fat mass

1- Causes dysfunctions in insulin-receptor interactions and intracellular kinase activity leading to insulin resistance
2- Reducing the effects of Insulin, increasing the turn-over of triglycerids, free fat ascides and phospholipids in liver and fat tissue.
3- Increases the density of triglycerids, phospholipids and free fat ascides in muscle and organs
4- Blocking the receptor number and activity of PPAR-γ
5- Inhibation of production of Glut-4 glucose transport protein.

Diab.Care 24(4):663,2003

ADIPONECTIN (EXON-2)

This hormone is secreted parallel to white fat tissue mass. It is the only precursor secreted from fat tissue with proven effects of preventing atherosclerosis, insulin resistance and cardiovasculer accidents [14].

1- Secreted from Adipocytes
2- It is a counter-hormone of insulin resistance
3- Effecting over 3927 chromosomes, reducing insulin resistance and atherosclerosis
4- Reduces density in morbid obese patients and Type 2 Diabetes
5- Increasing PPAR-γ cativity and reducing atherosclerosis and insulin resistance
6- Increasing intracellular kinase activity and reducing insulin resistance
7- Inhibates cellular inhibators like TNF-α, IL-6, PAI-I and alikes, playing an important role in reducing the insulin resistance. It slows down or stops the development of Diabetes resulting from obesity.

TNF-α

It is secreted from tumorous tissues, fat tissue and cells under toxic influence. It leads to insulin resistance. The effects ofthis hormone are seen in Table 8 [15].

Table 8. Products of visceral fat tissue, insulin resistance and TNF -α

PRODUCTS of VISCERAL FAT TISSUE and INSULIN RESISTANCE

TNF - α

- It increases parallel to white fat tissue mass
- It causes insulin resistance parallel to it's increased levels
- Inhibates the nuclear factors in muscle nad fat tissue, causes insulin resistance.
- Inhibates intracellular glucokinase activity, causes insulin resistance
- Inhibates GLUT-4 protein production
- Inhibates PPAR-γ activity, causes insulin resistance, Diabetes and atherosclerosis.
- Corrupts glucose depending secretion of insulin from β - cells, causes IGT and Diabetes

Diabetes.51:2964, 2002

HSD- I (Hydroxy steroid dehidrogenase - I)

It is secreted from fat tissue parallel to fat mass. It increases the transformation of cortisol to active cortisol in fat tissue. Cortisol increases in fat tissue. This leads to;

- The transport and production of free fat ascides and triglycerides from liver and fat tissue increases leading to fat accumulation in organs. (Insulin resistance)

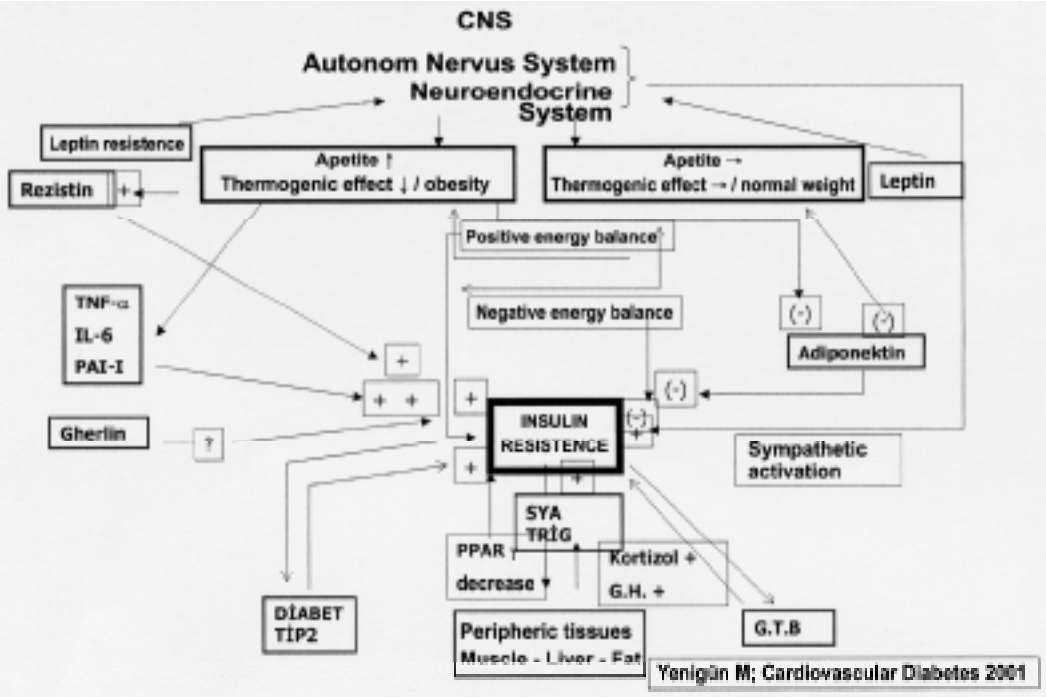
- Increases glucogenolysis and causes insulin resistance

- Causes dysfunctions in receptors and intracellular kinase pathways, resulting in an increased state of insulin resistance.

- Apetite increases, Leptin resistance develops, fat mass increases, adiponectin gets inhibated. TNF-α, IL - 6, Resistin levels increase.

-Inhibates PPAR-γ receptor activity

Table 9. Fat tissue and Insulin resistance relations



THE BENEFITS of WEIHGT LOSS in TYPE 2 DIABETES MELLITUS

It is common knowledge that weight loss reduces, even prevents the risk for developing of IGT and Diabetes. The benefits of losing weight are;

- Reduced hepatic glucose supply and output, improvement in hyperglycemia, decreased insulin secretion, reduced insulin resistance

- Improvement in blood lipid levels

- Improvement in blood pressure

- Reduced risk of thrombosis and atherosclerosis

- Need for oral antidiabetics and insulin reduces

Table 10 illustrates the data from UKPDS showing the improvement in metabolic parameters in diabetic individuals gained by reduction of body weight 4-6 kilograms.

Table 10. Effects of 3 month long diet in newly diagnosed Type 3 diabetics

	Male n= 1691	Female n= 1215
Body mass index (kg/m2)	❑1.5	❑1.7
Weight (kg)	❑4.6	❑4.4
Fasting Glucose (mg/dL)	❑54	❑53
HbA1c (%)❑2.0	❑1.8	
Fasting Insulin (mU/L)	❑2.0	❑1.9
Total cholesterol (mg/dL)	❑11	❑3.0
LDL cholesterol (mg/dL)	❑9.0	❑3.0
HDL cholesterol (mg/dL)	❑1.0	❑0.4
Triglicerid (mmol/L)	❑0.4	❑0.2

UKPDS 45, Diabet Med 2000;17(7):518-23

CAN WEIGT LOSS PREVENT OBESE INDIVIDUALS FROM DIABETES ?

This question can be answered quite positively as yes.

Data from previous and still ongoing studies shows that reducing body weight through diet or drogs reduces development of diabetes in obese individuals. In Malmö study we even witness that weight loss might reverse Diabetes to IGT. Improved life standards, exercise, diet weight loss of 4-6 kilograms, can actually prevent the development of Diabetes 30-60%. Table 11 illustrates an summary of data from studies about the relation of weight loss and Diabetes [16,17].

Table 11. Studies about weight loss and prevention from Diabetes

- FINNISH Diabetes Prevention Study: 6 years 522 individuals
  - -Average weight loss 4.6 kgs
  - -Incidence of Diabetes reduces 58 %
- MALMÖ Feasibility Study: 6 years 6959 individuals
  - -Average weight loss 2.3-3.7 kgs
  - -50% of patients with IGT revers eto normoglycemia
  - -Mortality reduces 33 %.

- DA QUING Study : 6 years 577 individuals
  - -Average weiht loss 2.95 kgs
  - -Incidence of Diabetes reduces 31% in diet group
  - -Incidence of Diabets reduces 46% in diet + exercise group

- DIABETES PREVENTION PROGRAMM (DPT): 5 years, 3819 individuals
  - -Weigt loss in Metformin group 2.2 kgs
  - -Weight loss in life style change group 4.3 kgs
  - -Diabetes prevention in Metformin group 31%
  - -Diabetes prevention in life style change group 58%

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