Blood sugar values, normal and diabetic

The current norms for blood glucose are shown in the following table. The upper limit for normal levels of blood glucose is currently set at less than 5.6 mmol/l while the reference level 2 hours after a glucose load is less than 7.8 mmol/l.

Note that interpretation of the data is "temporary". Glucose levels swing somewhat from day to day and from individual to individual. Therefore, if high glucose levels are found, it is advised that measurement should be repeated on the following three days. Only then should hyperglycemia be noted as an enduring symptom and treatment started.

Fasting glucose levels between 5.6 mmol/l and 7.0 mmol/l indicate impaired glucose tolerance (IGT) while higher levels signify diabetes. IGT can be viewed as "pre-diabetes" as most individuals in this group develop diabetes type 2 with time.

In 2003 an expert group suggested reducing the cut point for impaired glucose tolerance from 6.1 mmoles/l to 5.6 mmoles/l. This is expected to increase the number of individuals diagnosed as prediabetics by about 20%. Many of these people have a large risk for development of diabetes type 2 later in life. Therefore, they should be advised to revise their lifestyle and work for reduction of their hyperglycemia.

Fasting blood glucose levels are proposed as the leading indication of the metabolic state. This is a rapid, inexpensive and accurate measure of the
individual's metabolic situation. The committee suggested that fasting blood sugar be determined every 3rd year after reaching 45 years of age. A glucose tolerance test is deemed unnecessary as long as fasting glucose does not exceed 5.6 mmoles/liter.

**What's wrong with having a little extra blood sugar?**

**Glucose intolerance and the development of disease.**

The suggested blood glucose standards are based upon statistical analysis of the correlation between of blood glucose levels and the development of pathological states. Among these is retinopathy, which can lead to blindness. One might have expected a linear relationship between the level of blood sugar and the development of glucose-related diseases. However, this is not the case, as shown in the next figure. Data from three independent studies are shown in which elderly Americans, Pima Indians and Egyptians were observed. These groups are known to be especially prone to development of diabetes type 2. In all cases, an abrupt increase in the frequency of retinopathy was noted when blood sugar levels exceeded 6.0-6.1 mmol/l. This toxic effect of glucose may result from sorbitol formation or follow glycation of proteins, a non-enzymatic coupling of glucose to proteins.
Classification of diabetes mellitus

Most diabetic patients fall into one of two classifications, diabetes type 1 and diabetes type 2. In the USA and Europe about 80% of all diabetic patients have the type 2 variant.

(American Diabetes Association 1998)

1. Type 1: β-cell destruction usually leading to absolute insulin deficiency.
2. Type 2: Variation from insulin resistance and increased insulin levels to a dominant defect in insulin secretion with insulin resistance.
3. >40 well-defined types of diabetes.
4. Gestational diabetes:
   Any degree of glucose intolerance first noted in pregnancy.

Patients with diabetes type 1 must receive insulin to survive. Patients with type 2 diabetes and glucose intolerance are best treated by learning to control their own metabolism through proper diet and motion. In addition, many use metformin to reduce the liver's glucose production.

Specific treatment of the detailed cause of diabetes type 2 is seldom possible. It would be of great advantage to have exact knowledge of the origin of glucose intolerance and diabetes type 2 in each patient. More than 40 differing causes have been found in some very few cases. These mainly involve enzyme mutations. This is an active research area and may, with time, lead to advances in treatment.

Gestational diabetes is a passing hyperglycemia in pregnancy. This is a genetically determined condition and is handled without insulin treatment. Women who acquire gestational diabetes often develop diabetes type 2 later in life.
**Diabetes type 1**

**Insulin was first identified in pancreatic extracts by Banting and Best in 1922.** The first patient who received insulin was 14-year-old Leonard Thompson, also in 1922. Diabetes type 1 was a fatal disease prior to Banting and Best's work. Treatment of diabetes type 1 with insulin is still not economically possible for many patients in underdeveloped countries.

Diabetes type 1 results from an autoimmune destruction of the β-cells of the pancreas. It has been most commonly accepted that this is a genetically controlled process associated with HLA alleles. However, there is a age-dependent spreading of the disease and this has changed with time. Increasing evidence points to a combination of factors leading to beta cell destruction. The disease most commonly develops before 20 years of age as is shown in the figure to the left. However, incidence (cases/100,000) of the disease has changed in the latter half of the 20th century. Patients develop diabetes at an earlier age and the frequency has increased. This implies that there are other factors than the genetic which lead to development of diabetes type 1. The data is from Norway and can be found in "The Rise of Childhood Type 1 Diabetes in the 20th Century", Medscape or in the original publication (Diabetes 51, 3353, 2002).

A further indication that factors other than the genetic are involved in development of diabetes type 1 is shown in the next figure. The data are also from Norway and show a clear decrease in the frequency of diabetes type 1 in adults during World War 2 (cases/100,000). This data strongly suggests that social and economic factors are involved in development of the disease. The scanty diet and need for physical activity experienced during the war led to weight reduction in many adults. Overweight just might be a factor in
development of both diabetes type 1 and type 2.
Autoimmune attack on the Langerhans Islets

It has been commonly assumed that antibodies and T cells specifically attack beta cells, leading to insulin deficiency and destruction. However, in a recent publication, Shawn Winer et al have shown that Schwann cells which surround the Langerhans islet are autoimmune targeted and destroyed before the autoimmune attack on beta cells and loss of beta cell activity. It appears that antigen-presenting cells move from islets to the pancreatic lymph node where cell-specific antigens are produced. These attack Schwann cells surrounding the islets, destroying the Schwann cell capsule which surrounds islets. Beta cell destruction follows. (Nature Medicine 9, 198-205, 2003).

Diabetes type 1 patients are today completely dependent upon injections of insulin to sustain life. Current research is aimed at developing oral agents capable of activating the insulin-signal pathway downstream of the insulin receptor. In this way the need for injected insulin may perhaps be eliminated in the future.

Why don't we replace lost β-cells?

One might think that we could replace destroyed β-cells and restore insulin secretion and control of metabolism. After all, blood cells, skin and intestine do not disappear after loss of tissue. This was the question a group of researchers at Harvard put forward in a recent study. They investigated generation of β-cells in mice and looked for formation of new pancreatic islets in adult animals. Surprisingly, they found that no new islets could be identified. In adult mice, β-cells are formed only by self-duplication and appeared not to arise from stem cells. The permanent loss of β-cells seen in diabetes type 1 may, therefore, occur because only preexisting β-cells give rise to new insulin-producing cells in the adult. The loss of insulin producing β-cells seen with time in diabetes type 2 may
also develop through this mechanism. Go to the original article for more information. Click here to call up *"Adult pancreatic β-cells are formed by self-duplication rather than stem-cell differentiation", Dor et al, Nature 429, 41 (2004).*

**Diabetes type 2**

Diabetes mellitus type 2 arises from a reduced response of target tissues to insulin (so-called insulin resistance). Insulin levels are often quite high in early type 2 diabetes. The etiology of insulin resistance remains unclear, although many hypotheses have been set forth. I will go into these later, but there is a very clear association between overweight (BMI 25-30) or obesity (BMI>30), the metabolic syndrome and development of diabetes type 2. A genetic factor is also clearly involved. Many ethnic groups are predisposed for the disease. More detailed information about the causes of and classification of diabetes mellitus can be found here.

Diabetes type 2, earlier called "maturity-onset diabetes", typically develops over a period of many years. It usually begins with overweight, goes through a period of glucose intolerance, and ends with the full-blown diabetic state. In contrast to diabetes type 1, the disease develops slowly and goes through several stages as shown in the following figure.

Obesity seems to be the most common factor initiating development of diabetes type 2. The patient goes through a period of increasing insulin resistance during which the body compensates by producing higher levels of insulin after meals. Usually, the patient is unaware of his or her situation. Following a period of many

![Natural History of Type 2 Diabetes](chart.png)

*IGT=impaired glucose tolerance
Adapted from International Diabetes Center (IDC), Minneapolis, Minnesota.*
years, the pancreatic β-cells no longer manage to continue their enhanced insulin secretion. Insulin levels fall in the face of continuing insulin resistance, resulting in increased fasting blood glucose levels and markedly increased post-meals levels of plasma glucose. It has been suggested that the insulin-producing β-cells are subject to attack even before this stage.

It should be noted that the global wave of obesity we now experience applies to young children too. Social factors (fear of kidnapping, parents who drive kids to school and after-school activities, passive TV and PC use, etc.) contribute to reduced physical activity and obesity in children. Simultaneously, energy intake is often increased through an ever-increasing consumption of fast foods, soda pop, sugar coated breakfast food, snacks and confection. The decreased physical activity coupled to increased food intake must lead to pronounced weight gain. These energy-rich foods appear not to function normally in the appetite-controlling mechanism. The reason for this is not yet clear but is the subject of much research. Diabetes type 2 in young children (formerly limited to adults) is now a serious and growing problem. Control of the long-term symptoms of diabetes type 2 will be a difficult and very expensive problem in the coming decades.
A Simplistic Approach to Weight Regulation

There are very many factors involved in normal weight regulation. However, the end result is the consequence of the balance between the amount of energy in the ingested food and the amount of energy used. Hormone levels, altered hormone receptors, mutated metabolic enzymes; all of these do influence appetite and energy use. However, the bottom line is, you are what you eat (and do not burn). Look at the next figure (modified after Marks, Marks and Smith, Basic Medical Biochemistry). The activity levels shown here correspond to those that are normal in a modern society. A young male student uses most of the energy in his food to support normal body functions (basal metabolism or BMR). Only about 20% of the consumed energy go to support physical activity.

If one leads a more active life (cycling to work, using stairs instead of the elevator, some sports after studying), the total daily energy use increases to about that level that the average person used for 100-150 years ago. It is estimated that, at that time, both men and women used about 3000 kcal/day for the usual daily chores. Note that at this activity level physical activity still accounts for not more than 25-30% of the total energy used daily.

A heavy activity level, as judged by our modern standards, will increase energy use to around 3500 calories/day. By the way, lumberjacks using axes and hand saws are said to have used about 5000 calories per day!
The drawings on the right show the result of balancing (or not balancing) food intake with energy expenditure. Clearly, eating more than one uses is "expansive", a balanced food and energy use results in a stable body mass while under nutrition leads to weight loss.

"The Easy way and the hard way...

Most experts believe that a sedentary or passive life style is the best explanation for the trend to overweight. That is, weight gain is more closely related to energy use than energy intake. What has changed in the past decade?

A recent editorial in Mayo Clinical Proceedings listed some examples of sedentary and active ways of doing things. Many of the recent advances (read labor-saving) in our daily environment reduce energy utilization. If you make some assumptions you can calculate the approximate difference in total energy use between the "easy and hard" ways of doing common tasks. This lies somewhere around 10,000-15,000 kcal every month or two. That is just about the equivalent of 1-1.5 kilograms of body fat. Few of us take this into account when we plan our meals! Doing things the active way, a partial switch to a plant-based diet with no more than 30-35 calorie-% fat and moderate daily motion for between 30-60 minutes should help keep the fat away for many people.

We all have heard that "our western way of life" leads to the physical downfall that we have experienced during the past 10-20 years. The fact is that
obesity is a global phenomena linked more to physical activity than race and culture.

WHO has stated “At the other end of the malnutrition scale, obesity is one of today’s most blatantly visible – yet most neglected – public health problems. Paradoxically coexisting with malnutrition, an escalating global epidemic of overweight and obesity – “globesity” – is taking over many parts of the world. If immediate action is not taken, millions will suffer from an array of serious health disorders”.

Let us look at rates of obesity in a global perspective. We have most data from USA and England, but also some data from South America and the Pacific area. About 25-30% of the populations of USA and England have now a BMI of 30 or more. We see the same trend in a little island in the Indian Ocean (Mauritius) and the trend in Brazil is not much better. The most striking figures come from the Pacific region. Here, around 70% of the adults on some islands are obese. The prospects facing health officials and physicians are grim.

Obesity, a Global Problem
The situation is well-described in the following quotations from Paul Zimmet's article entitled:

"The global scope of diabetes and obesity -- an epidemic in progress: paradise lost"

"... Type 2 diabetes is poised to become one of the major challenges to public health in the 21st Century and will result in a huge economic burden, particularly in developing nations, through premature morbidity and mortality.

...there will be more than 230 million people with diabetes by 2010. The majority of the new cases will be those with type 2 diabetes.

... Type 2 diabetes is the tip of the iceberg of a cluster of cardiovascular disease (CVD) risk factors, including obesity, hypertension, and dyslipidemia, otherwise known as the "Metabolic Syndrome," "New World Syndrome," or "Deadly Quartet." The natural consequence will be an epidemic of cardiovascular complications, such as coronary heart disease and stroke as well as microvascular complications.

... Over 60% of the adult population of the United States and Australia are either overweight (body mass index [BMI] of 25-29.9 kg/m2) or obese... In some developing countries -- as well as in disadvantaged groups in developed countries (Mexican Americans, African Americans, and Australian Aborigines) -- an even more extreme situation exists. In Samoa and Nauru, more than 70% of adults fit the obesity criteria.

... An important and alarming feature of the diabetes epidemic is that type 2 diabetes is increasing in these younger age groups. In China, Japan, and in the Pacific Islands, more than 70% of children presenting with diabetes have the type 2 form.

... Obesity and lack of exercise have been implicated in this trend, that has been labeled as "Nintendonization". Children are often driven to and from school and then come home and race to the computer or computer-game station instead of playing games or sports outdoors".

Paul Zimmet MD, PhD

60th Scientific Sessions of the American Diabetes Association
June 10, 2000
Why don't we eat less?

...and a somewhat subjective answer.

The amount of food we consume each day is regulated by what we call appetite; the desire to eat. The hypothalamus is the central coordinator of signals relating to hunger and satiety. The genetic basis for this very complicated process has developed over a period of millions of years. The following figure shows actual

![Estimated Energy Expenditure](image)

values for energy expenditure for modern man (to the right) and estimated values for many of our prehistoric ancestors. Rates of both basal and total metabolism are given. Both BMR and total metabolism seem to have been more or less constant from earliest prehistoric times to those seen in now-living "primitive" people (groups who base their existence on hunting and gathering). An energy expenditure of around 200 kJ/kg per day calculates out to about 3200 kcal/day for a 70 kg person. The only exception shown in the figure is the modern city dweller, whose energy use lies around 2000-2200 kcal/day.

About 150 years ago most people used around 3000 kcal per day to come through a day's chores. Work was done manually. She washed, cleaned and raised children without a car, a washing machine, vacuum cleaner, or a dish washer. Food was prepared from raw products on a wood stove. He built and worked on the farm without tractors, harvesters and chain saws or in a factory or mine with heavy manual tasks. Modern life goes back no further than to the beginning of the 20th century. Modern or "post-modern" styles of life have existed for no more than 100 years for people in industrial societies and far less for those in developing countries. The current imbalance between intake of food and expenditure of energy may well have followed the introduction of powered labor-saving devices during this short period. Genetic adaptation to changes in environment occur slowly through many generations. Stable genetic adaptation to new environments in whole populations do not occur "overnight".

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Now, the fact is that the frequency of obesity has not increased linearly during the past century but quite rapidly during the past decade. This is clearly shown in the next figure from the USA. Remember, obesity is defined as having a BMI of 30 or more. In 1991, only 5 states had a population in which 15% or more were obese. By 2000, all but one state could boast of this. In most of these over 20% of the population had an BMI over 30. Between 60-70% of the American population was either overweight or obese in 2002.

Overweight is probably as large a threat to health as hunger in today's strange world. One of my colleagues was recently in India. He reported that the "man on the street" in southern India was as thin as we in the West usually imagine him to be. However, obesity was very frequent at Indian airports. Good economy, easily attained food, a car and other labor-saving devices lead to weight gain, metabolic syndrome and poor health.

If we go back to the actual figures from the United States in the period 1991-2000 and look at the incidence of diabetes we see an increase that is parallel to the spreading of obesity. Ninety percent of these cases are type 2 diabetes. Overweight also increases the risks for hypertension, dyslipidemia and coronary disease, renal failure, retinopathy etc.
Sugar and Health

According to most sources, the yearly intake of sugar has risen from 4-5 kilogram in the 1850s to about 40-50 kilos in the 1990’s. Forty kilos equal about 400 kcal/day or around 15-20% of the energy needed to maintain normal activity. Much of this sugar comes from soft drinks. These contain approximately 30-40 sugar bits per liter! Sugar is used as a "spice", giving a proper taste without a thought about its energy content.

Now, the fact is that many individuals consume much more sugar than the alleged 40 kilograms yearly. That figure often includes only "table sugar" or sucrose. In reality, soft drinks and cakes contain a lot of monomeric sugar (fructose and glucose) made from corn syrup. While the officially recognized sugar consumption in the USA in 1997 was 33 kg/person annually, the actual total sugar consumption was over 60 kg/person/year. This is shown in the next figure from the work of Elliott et al. Production of high fructose corn syrup began in the '70s. While it is quite true that sucrose intake was reduced in the following years, the total sugar consume increased dramatically. Total glucose and fructose, derived from sucrose and corn syrup increased by almost 30% during these 27 years. The high sugar consume is a major factor in increased caloric intake. Perhaps even more important is the very rapid and metabolically uncontrolled metabolism of fructose. Both of these factors contribute to hepatic triglyceride production and augmented plasma triglyceride levels. There is a close correlation between plasma triglycerides and artherosclerosis and development of cardiovascular disease. You can get more information about metabolism of fructose by clicking here.

In the USA, agricultural subsidies have increased production and consumption of sweet and fat food. Medscape has presented a good discussion on this in an article from the National Institute of Environmental Health Sciences. Click here to access that article.
Metabolic Syndrome or Syndrome X

The relationship between diet, metabolism and poor health expressed by the term "metabolic syndrome" was noted simultaneously by cardiologists and endocrinologists about 10-15 years ago. While the numbers of CVD patients was decreasing, an increasing percent of new cardiac patients were found to be overweight, have increased blood sugar, dyslipidemia and hypertension. These symptoms were also noted in the ever-increasing number of patients with diabetes type 2. This condition was called "Syndrome X" or metabolic syndrome.

There are several definitions of this syndrome. The ATP III (Adult Treatment Panel III; a NIH expert committee) has defined metabolic syndrome shown in the next figure (reference values in italics). Those fitting 3 of the 5 criteria have metabolic syndrome. These criteria are objective, being based solely on observations seen in many thousand patients. Overweight is characteristic of most of these, especially those with an accumulation of fat surrounding the intestines (central obesity). It has been suggested that this is because of the relatively large metabolic activity of this tissue. A more recent suggestion is that abdominal fat produces cortisol that may influence metabolism. A newly discovered peptide hormone, omentin, which increases food consumption is also produced here. Many of these individuals show high levels of serum total triglycerides and this is often observed in overweight. High density lipoprotein levels (HDL) are often lower than normal. Interestingly, LDL levels do not correlate well with the pathological changes seen in metabolic syndrome. However, a shift to large lipid-rich LDL particles is often seem. Hypertension is

**Definition of Metabolic Syndrome**

**Syndrome X**

Three or more of the following criteria:

- **Central obesity** (waist circumference >102 cm (men), >88 cm in women)
- **Hypertriglyceridemia** (≥1.69 mmol/l)
  - (<20 yr, <1.6; <30 yr, <1.7; <40 yr, <1.8; >50 yr, <2.1)
- **Low HDL** (HDL < 1.04 mmol/l (men)
  - <1.29 mmol/l (women)
  - Men, 0.7-1.8; women, 0.8-2.0)
- **Blood pressure** ≥130/85 mm Hg
- **Treatment goal = 140/80**
- **High fasting blood glucose** (≥6.1 mmol/l)
- <6.1 mmol/l

ATP III (NIH Report 61-3670, 2001)
common in metabolic syndrome as is hyperglycemia. Dependent upon the level of blood glucose, these patients can be classified as having impaired glucose tolerance (IGT) or diabetes type 2.

The scope of the metabolic syndrome problem is enormous. Weight gain is common among older persons with a gradually increasing BMI from 30-40 years of age. This correlates well with development of metabolic syndrome as shown in the next figure from the USA. This data is not current. The percent of the population with metabolic syndrome and the subsequent health problems is much higher today. There is now a growing tendency for children, both in the USA and Europe, to develop glucose intolerance (IGT) and diabetes 2 parallel with obesity.
Weight reduction and diabetes type 2

The importance of overweight in the development of metabolic syndrome and diabetes type 2 cannot be overrated. Simply dieting and reducing weight can be sufficient to improve a patient’s situation. This figure from Medscape/Diabetes Care shows the effect of weight loss on the response to a 75g glucose load. After 12 weeks of dieting, fasting glucose levels were reduced as were the plateau levels following a glucose load. We know from this and many other studies that the difference noted is dependent upon increased sensitivity to insulin. In other words, weight loss often leads to decreased glucose resistance and a normalized metabolism.
Global perspectives of the incidence of diabetes

Predictions of the global frequency of metabolic syndrome, insulin resistance and diabetes are frightening. The consequences of urbanization and overweight are much more threatening than the AIDS/HIV epidemic. One of many estimates of the spreading of this global epidemic are shown in the following figure. Most of the increase in diabetes will be that of type 2. Overweight with associated insulin resistance and metabolic syndrome will lead to an almost 50% increase in the number of individuals suffering from diabetes within the current decade. Over 200 million persons will be involved. Most of this expansion will occur in developing countries where health services will be unable to cope with the coming situation. Without indispensable guidance and treatment, these people will develop coronary and vascular disease, chronic kidney disorders, hypertension and the many other complications of diabetes. Predictions for the middle of the century indicate that at least 300 million persons will develop diabetes type 2.
Genetic background is a strong component in the development of type 2 diabetes. People of western European origin are less sensitive to the effects of overweight than non-Europeans. In the USA, blacks and Latinos have a higher frequency of diabetes type 2 than whites. Asians, especially Chinese and Japanese, develop metabolic syndrome and diabetes type 2 at lower body weights than whites. Thus, these groups develop diabetes 2 in the BMI range from 25-30.

<table>
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<tr>
<th>Population grouping</th>
<th>Region</th>
<th>Percentage prevalence</th>
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This "puzzle" of sensitivity to diet and development of type 2 diabetes was taken up in a recent article by Jared Diamond in *Nature*. A figure from this article is presented below. Prevalence of diabetes is relatively low in Europeans and native people living in their accustomed environment. However, native people who convert to a western diet or urban life present a markedly increased incidence type 2 diabetes. Genetic variation can explain differing frequencies of diabetes development in diverse racial groups. However, development of type 2 diabetes among urbanized groups must be a response to the environment. Genes do not change so quickly!

One explanation for this has been the development of a set of "thrifty genes", a genetic adaptation to a poor milieu with a meager diet. A switch to an urban diet and activity level is suggested to rapidly lead to obesity and associated illnesses in such people. Please go to the original article for discussion of this data.

An excellent review article concerning the development and possible causes of the global diabetes epidemic can be found here. Medscape (May 2003) offers a CME entitled "The Obesity Epidemic: Prevention and Treatment of the Metabolic Syndrome".
Insulin resistance, the key to diabetes type 2

The next figure comes from a study of glucose levels in obese and control individuals after meals. The overweight persons depicted here were on the way towards developing glucose intolerance, but still had control over their blood sugar levels. We can clearly see that obesity is accompanied by insulin resistance. The obese persons produced more insulin after meals than controls to counteract this. In this way they can counteract their insulin resistance and regulate glucose uptake and hepatic glucose production.

I have previously explained that diabetes type 2 develops in response to a loss of reactivity to insulin at target organs. To counter this, the pancreatic β-cells produce more insulin to counter the decreased target organ sensitivity. Initially, metabolic control will be normalized through this mechanism. However, with time, the individual will develop impaired glucose tolerance and diabetes type 2.
We can identify two processes in which insulin resistance is involved in the next figure. The panel on the left shows that glucose disposal (glucose taken up from the blood) is reduced in type 2 diabetes. This indicates that muscle and adipose tissue take up less glucose in these patients than control persons, leading to hyperglycemia after meal.

Another central function of insulin is inhibition of hepatic gluconeogenesis. Remember that it is the balance between glucagon and catecholamines on one side, and insulin the other that directs hepatic gluconeogenesis and release. Glucagon and the catecholamines stimulate glucose production and glycogenolysis when blood glucose levels fall: insulin inhibits gluconeogenesis when there are adequate levels of glucose in the blood. In the right-hand panel we can see that hepatic glucose production is less sensitive to insulin in diabetes type 2. In spite of high blood sugar levels, the liver produces glucose and releases it to the circulation. People suffering from diabetes synthesize glucose in spite of the fact that blood glucose levels are elevated! Therefore, treatment with a glucose synthesis inhibitor, metformin, is often started in addition to adjusting to a new life style.

Insulin Resistance in Type 2 Diabetes

![Graphs showing glucose disposal and hepatic glucose production vs. plasma insulin levels for control and type 2 diabetes patients.](image)

Redrawn from Medscape 2000
How does insulin resistance develop?

The key to this problem seems to lie in the interaction between adipose tissue and skeletal muscle. In "the old days", we looked on fat as a relatively inactive, not especially attractive part of our bodies. We now know that adipose tissue is metabolically quite active and is one of the body's most important endocrine organs. No less than 14 peptide hormones have been found in adipose tissue. In the past few years three of these, leptin, adiponectin and resistin have received most attention.

Leptin seems to have many actions; it is involved in thermoregulation, bone metabolism, fatigue and especially appetite regulation together with insulin and blood sugar. Current opinion (spring 2004) seems to be that leptin is a signal of reduced energy and stimulates hunger as a result of reduced release from adipocytes. Release of leptin appears to be triggered by the rise in insulin levels seen after a meal. Together, insulin and leptin act centrally to reduce hunger.

Resistin has been implicated in regulation of insulin sensitivity (and insulin resistance) in muscle and adipose tissue. Adiponectin is also possibly involved in regulation of target-cell's sensitivity to insulin.

One can conclude that adipose tissue is actively involved in regulation of energy homeostasis through two major functions:
1. As a storage tissue for excess nutrients and as a source of energy reserves to all of the body’s organs (remember ketogenesis and the brain).

2. As an endocrine organ involved in regulation of appetite and insulin sensitivity.

The first world congress on insulin resistance was held in Los Angeles, California in 2003. Several theories concerning impairment of responses to insulin were presented at the congress. You can call up a review of the highlights from that meeting by clicking here.

Central Control of Appetite

Those of us who studied medical biochemistry a few decades ago learned that appetite was controlled centrally through glucose-sensitive cells in the brain or hypothalamus. Indeed, this is still a "fact". However, we now know that many other factors are involved. Initially, insulin and recently leptin were seen as the major elements controlling appetite. The levels of these are affected by the food we eat, our activity level and our fat stores. Central control of appetite is discussed in detail in a review article in Nature 404, 661-671, 2000. Click here if you have a subscription to this journal. The next figure, taken from this article, shows the roles of insulin and leptin in this system. I have earlier emphasized the balance between food consumption and physical activity. These factors define "energy balance". While we really are not aware of regulation of appetite, most people managed to hold this balance and a more or less constant body
weight before all of our "labor-saving" devices became common. This implies that a very well regulated system must exist. The combined effects of insulin and leptin in the central nervous system appear to fine-tune our urge to eat, leading to a decreased food intake at weight gain and increased appetite following physical activity or weight loss. Please go to the original article if you wish follow this further.

More recently, several additional peptide hormones that couple the digestive system to appetite regulation have been identified. These are ghrelin, released from the stomach and the intestinal hormone PYY

\[ \text{PYY}_{3-36} \]

These hormones interact with insulin and leptin sensitive neural cells in the brain. These produce an effect through interaction with hypothalamic neurons producing neuropeptide Y (NPY) and the Agouti-related protein (AgRP) (the GO system) or by activating the melanocortin system: (the STOP system). The balance between "stop and go" signals effects neurons that regulate the sense of hunger and appetite. Insulin and leptin are thought to regulate long-term effects and body weight, while the hormones derived from the digestive system appear to regulate meal-eating on a short-term basis.

Please go to the original publication for more details: Nature 418, 595 - 597 (2002).