Secondary diabetes

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Diabetes is called "primary" when no known etiological cause is found and "secondary" when hyperglycemia is thought to have developed in relation to a known etiological factor. Our knowledge of how and why diabetes occurs is still evolving and in practice a clear distinction between primary and secondary diabetes is not always possible. It is believed that timely diagnosis of "secondary" diabetes and successful treatment of the causative factor might "cure" diabetes. At present, the vast majority of diabetic patients are classified as primary. Even in these patients, a number of life-style factors are responsible for precipitating diabetes. Successful treatment of these factors improves glycemic control.

Pathogenesis

Present understanding of the pathological mechanisms allows classification of diabetes into two main types, Type I or insulin-dependent diabetes (IDDM) and Type II or non-insulin-dependent diabetes (NIDDM).

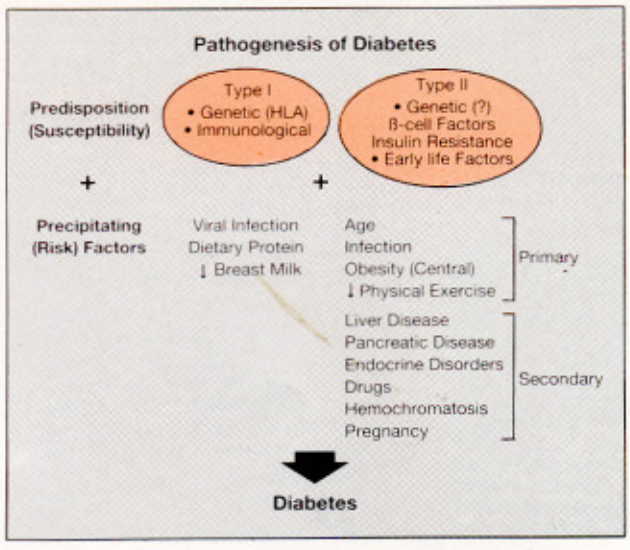
Secondary diabetes can be either IDDM or NIDDM

Though the latter is far more common. Both types of diabetes occur when *susceptible* individuals are exposed to *precipitating* factors *(Figure 1)*.

Type I diabetes results from immune/toxic destruction of pancreatic ß-cells, leading to severe insulin deficiency. The genetic susceptibility factors (HLA) and immune markers (circulating islet cell antibodies) in this condition are known but little is known of the precipitating factors, though many are suspected *(Figure 1)*.

Type II diabetes appears to be a more complicated disorder, and is probably a "mixture" of different conditions. It results from a variable interaction of insulin insensitivity of the peripheral tissues (resistance) and ß-cell dysfunction. Different organs ie, endocrine pancreas, liver, skeletal muscle, and adipose tissue, are involved in the pathogenesis, and abnormalities of the "counterregulatory" hormones (glucagon, growth hormone, catecholamines, etc) probably contribute to the metabolic problem. It has a long (many years) "prediabetic" phase during which blood sugar levels are normal but hyperinsulinemia is charateristically seen. In *susceptible* individuals, ß-cells are "exhausted" and hyperglycemia results, which further amplifies the basic pathologial problems (glucotoxicity).

Figure 1. Pathogenesis of Diabetes.



Susceptibilty to type II diabetes is believed to be genetic because it runs in families, but no genetic markers have yet been found. In fact, recent findings suggest that maternal factors (intrauterine nutrition, etc) modulate ß-cell function and influence development of diabetes in later life. In type II diabetes, some of the precipitating factors are well defined. These are usually associated with adverse life-style ("central" or "android" obesity, overnutrition, and poor physical activity). These are perhaps responsible for the recent "epidemic" of diabetes in certain populations. It could be argued that type II diabetes is "secondary" to these factors *(Figure 1)*. In fact, abnormalities of any of the multitude of factors described above could tilt the balance and cause diabetes which could qualify as "secondary" diabetes.

On this background, the present definition of "secondary" diabetes appears rather naive, because diabetes is ascribed entirely to the known "precipitating" factor. In some cases (acromegaly, Cushing's syndrome, etc) such factors could be very potent but such cases are very rare in clinical practice. Even such cases of "secondary" diabetes have an overlap with "primary" mechanisms.

The treating physician's job is to seek and treat such factors which will improve the prognosis for the patient even though successful treatment of the precipitating factor(s) does not "cure" diabetes.

Also, treatment of some factors is not always possible (eg, chronic pancreatitis, liver cirrhosis) but its diagnosis improves management of diabetes. Another classic example of primary diabetes with a well recognized precipitating factor is gestational diabetes. The latter occurs in susceptible women (ie, overweight, those with a strong family history, etc) during pregnancy. Glucose intolerance improves after delivery in many women, but they may become diabetic in later life (up to 50% became diabetic over 15 years in one series). This highlights the important contribution of both susceptibility and precipitating factors in the genesis of diabetes.

In the past, it was thought that patients with secondary diabetes did not suffer the microvascular damage but we now know that such complications do occur if hyperglycemia persists for long enough.

For the present discussion we will restrict to the definition of "secondary" diabetes given in the introduction *(Table 1)*.

Useful clinical pointers to secondary diabetes are shown in *Figure 2* which should help the physician suspect these conditions.

Pancreatic disorders

Chronic pancreatitis is the commonest cause of secondary diabetes. It constitutes perhaps less than 1 % of all diabetic patients, though in certain diabetic clinics in tropical countries it is more common. Even though endocrine pancreatic deficiency develops secondary to exocrine pancreatitis, it appears that susceptibility to diabetes (see pathophysiology above) certainly plays a role. Thus, a family history of diabetes is more common in these patients and association of both HLA and insulin gene polymorphism has been demonstrated in patients with tropical calcific pancreatitis.

1. **Pancreatic disorders**
   Chronic pancreatitis (Alcoholic, tropical, etc),
   Cystic fibrosis,
   Cancer, etc.
2. **Liver disorders**
   Cirrhosis,
   Chronic active hepatitis.
3. **Endocrine disorders**
   Acromegaly,
   Cushing's syndrome,
   Thyrotoxicosis,
   Glucagonoma,
   Pheochromocytoma,
   Conn's syndrome,
   Hyperandrogenism.
4. **Hemochromatosis**
5. **Drug-induced**
   Corticosteroids,
   Oral contraceptives,
   Thiazide diuretics and Diazoxide,
   Vacor and other
   pancreatic toxins,
   Cyclosporin A,
   Pentamidine.
6. **Genetic disorders**

Table 1. Common causes of secondary diabetes

There are two major types :
1. chronic alcoholic pancreatitis, and
2. tropical calcific pancreatitis.

Alcoholic pancreatitis

This is the most common form of chronic pancreatitis in the Western world. It usually affects middle-aged subjects. There is a long history of alcohol abuse and episodes of pancreatitis characterized by typical pain. Diabetes appears after many years, when pancreatic exocrine and endocrine reserves are severely diminished. Pain of pancreatitis might have disappeared by this point but steatorrhea is usually present. Clinical stigmata of chronic alcoholism, liver cirrhosis, and portal hypertension help in the diagnosis. Pancreatic calculi are frequently demonstrable on x-ray of the abdomen, and ultrasonography. In the initial stages, diabetes might be controlled by diet and oral hypoglycemic agents, but insulin treatment is usually necessary in more severe cases. Blood sugar levels tend to fluctuate widely because of various factors including irregularities in diet, associated liver disease, maldigestion and malabsorption due to exocrine pancreatic deficiency and glucagon deficiency. Severe hyperglycemia and hypoglycemia can occur within short periods of time, but ketoacidosis is not common. Appropriate dietary adjustments and treatment of associated pancreatic deficiency by oral pancreatic enzymes improve glycemic control.

Intractable pain due to ductal obstruction, cyst, or pancreatitis may necessitate surgical treatment. Surgical treatment usually has no effect on the natural history of diabetes.

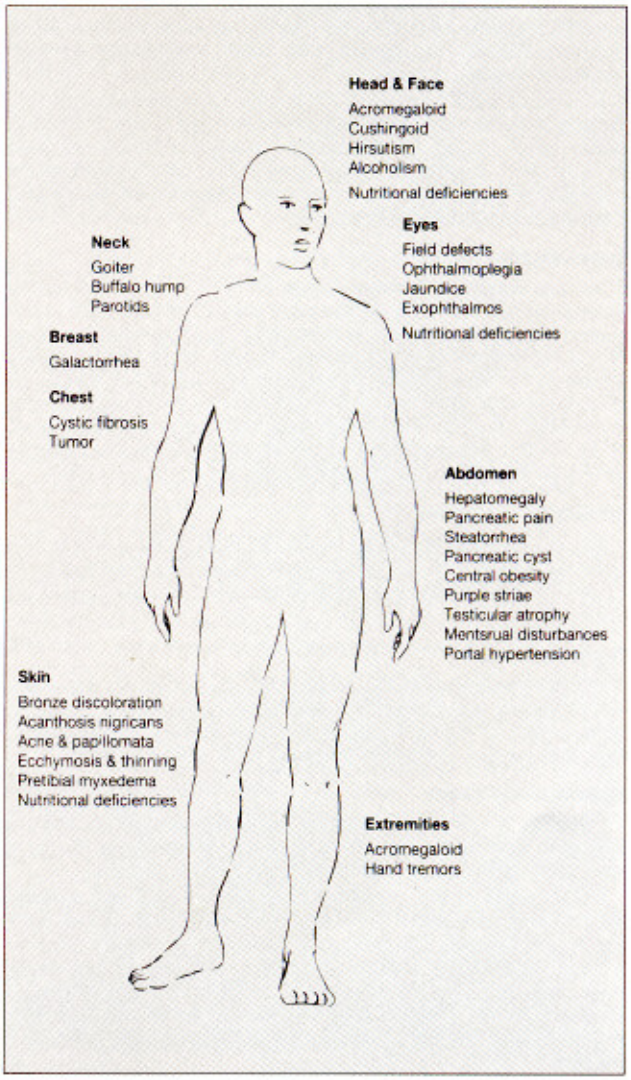
Tropical calcific pancreatitis (TCP)

This is a peculiar form of chronic pancreatitis seen in the tropical developing countries. It has been reported in the Indian subcontinent, South-East Asia (Indonesia), many African countries (Nigeria, Ivory Coast, etc) and in South America (Brazil). Patients are usually the rural poor, but it is also seen in the urban and the affluent. The most characteristic feature is the young age at onset. Pancreatitis usually starts before 15 years of age, very often in the first decade. It progresses relatively rapidly to severe pancreatic deficiency. Steatorrhea may not be apparent because of small dietary fat intake. Initial reports highlighted stigmata of severe malnutrition in these patients, especially in those of rural origin. This led to the suggestion that manutrition and cassava consumption were etiologically responsible (malnutrition-related diabetes, MRDM) but this is not agreed by all.

There is a good correlation between exocrine and endocrine loss on the one hand and residual ß-cell function and glucose tolerance on the other, suggesting that exocrine pancreatitis is an important factor in the genesis of diabetes. Glucose tolerance passes through the phases of normal, impaired gluose tolerance (IGT) and diabetes. Diabetes usually appears in the second decade of life, though younger patients are not unusual. Severity of diabetes is variable. Most poor patients present with severe hyperglycemia. Diet and oral hypoglycemic agents are useful in milder cases but insulin is usually required as disease progresses. A peculiar metabolic feature is the relative rarity of ketosis in these patients even with severe hyperglycemia and after stopping insulin treatment for prolonged periods of time (usually due to socioeconomic reasons). Such an immunity from acute metabolic complications leads to poor compliance with treatment. Many patients die relatively young due to metabolic (hyperglycemia) and infective (tuberculosis, etc) complications. Vascular problems of diabetes (retinopathy, nephropathy, and macrovascular disease) appear with increasing duration of diabetes and increasing age. Treatment is frequently influenced by socioeconomic factors. Many cannot afford insulin, and very few can afford oral pancreatic enzymes. Surgical intervention is usually for pain and probably has no effect on the natural history of diabetes.

It appears that both tropical and alcoholic pancreatitis might lead to cancer in some patients. Diagnosis of pancreatic cancer should also be suspected in (elderly) diabetic patients who have lost substantial weight and have other related symptoms (pain, obstructive jaundice, etc).

Figure 2. Clinical features suggestive of "secondary" diabetes.



Understanding diabetes

Liver disorders

The liver plays a central role in intermediary metabolism. Widespread liver damage, as in cirrhosis, reduces hepatic extraction of insulin from the portal circulation, leading to systemic hyperinsulinemia and insulin resistance. This precipitates diabetes in susceptible individuals. Hypokalemia of chronic liver disease contributes to diminished insulin secretion. Other aspects of glucose metabolism are also affected, particularly the ability of the liver to increase glucose output in the face of falling circulating glucose concentrations. These patients are therefore at an increased risk of hypoglycemia when on antidiabetic treatment. Peculiar problems associated with individual etiological factors of liver cirrhosis (chronic alcoholism, hepatitis B and other viral infections, etc) add to the difficulties in management of diabetes.

Impaired glucose tolerance and mild diabetes are present in 50-80 % of patients with established cirrhosis but a smaller number (± 30 %) show fasting hyperglycemia. It is suggested that these individuals with more severe diabetes were destined to develop "primary" type II diabetes.

Treatment of diabetes is by diet, oral sulfonylureas and insulin injections when necessary. Biguanides are best avoided because of the increased danger of lactic acidosis.

Endocrine disorders

Intermediary metabolism is delicately balanced by the actions of insulin and other "counterregulatory" hormones which include glucagon, growth hormone, glucocorticoids, catecholamines, thyroid hormones, etc. Excess levels of the counterregulatory hormones produce hyperglycemia by overcoming ß-cell reserve, especially in susceptible individuals. Numerical contribution of these syndromes to everyday diabetes is perhaps quite small. Diagnosis of these conditions is usually obvious because of the classic symptoms and clinical features of hormone excess.

The stages in the progression of glucose tolerance from normal to diabetes in these patients are very similar to those in type II diabetes. Initially, both glucose and insulin concentrations are normal; later, glucose concentrations are maintained within normal limits at the cost of hyperinsulinemia. In more advanced stages insulinopenia and progressive glucose intolerance develop.

Acromegaly

Glucose intolerance is seen in over 75 % of patients and fasting hyperglycemia in ± 25 %. In the initial stages, diet and oral hypoglycemic agents are useful in controlling hyperglycemia but once fasting hyperglycemia is established, insulin treatment is usually necessary. In earlier stages, successful treatment of acromegaly by surgery improves glucose tolerance and reduces the elevated plasma insulin levels. In those with insulinopenia, improvement is less dramatic. Octreotide treatment itself inhibits insulin secretion and therefore can cause hyperglycemia, though the effect is said to be transient.

Cushing's syndrome

Glucose intolerance is seen in over 90 % of patients and fasting hyperglycemia in ± 25 %. Successful treatment of cortisol excess by surgery or drugs ameliorates hyperglycemia in a substantial number of patients.

Thyrotoxicosis

Glucose intolerance is not uncommon in these patients, especially with increasing age. Control of toxicosis improves glucose tolerance. Development of thyrotoxicosis in a known diabetic patient aggravates diabetes and successful treatment helps glycemic control.

Hyperandrogenism

Evidence is now mounting that hyperandrogenism in women (hirsutism, central obesity, elevated serum testosterone levels) is associated with insulin resistance and could lead to diabetes.

Abnormalities of the menstrual cycle (anovulation) and infertility are frequently associated (polycystic ovary syndrome). Some show acanthosis nigricans. The effect of antiandrogen treatment (spironolactone, cyproterone acetate, estrogens, etc) on glucose-insulin metabolism and other cardiovascular risk factors in these women is not clearly known. These women also have increased risk of developing gestational diabetes. There is a considerable overlap with type II diabetes.

Glucagonoma, pheochromocytoma, and Conn's syndrome are very rare causes of diabetes in clinical practice.

Hemochromatosis

This is associated with deposition of iron in liver, pancreas, and other tissues including skin and gonads. Classical bronze discoloration of the skin, hepatomegaly with abnormal liver function tests, and impotence at presentation should raise the suspicion of hemochromatosis in a diabetic patient. It is not a common condition but it is useful to remember that glucose intolerance is seen even in patients with tranfusion-associated iron overload (thalassemia, etc) and in certain communities in Africa who drink beer brewed in iron vats. Iron overload causes both peripheral insulin resistance and progressive ß-cell failure. Associated pancreatic and liver involvement can produce problems during treatment of diabetes similar to those described above. Successful treatment of hemochromatosis by repeated phlebotomy and iron-chelating agents improves glucose tolerance to some extent.

Drug-induced

A number of drugs in common use can alter glucose tolerance, either by causing insulin resistance or by ß-cell dysfuntion. Some destroy ß-cells, causing acute insulin deficiency. Common examples of drugs which reduce tissue sensitivity to insulin include corticosteroids, oral contraceptives, thiazide diuretics, diazoxide, adrenergic agonists and antagonists. On the other hand, vacor (a rodenticide), pentamidine, and cyclosporin A seem to cause ß-cell dysfunction or destruction. Susceptibility of the individual (family history of diabetes, previous history of gestational diabetes, other genetic and immunological factors) seems to play a part in inducing glucose intolerance. Whenever possible, substitutes with a safer record with respect to glucose metabolism should be used in such susceptible subjects. In clinical practice, perhaps the most dramatic effect is that of corticosteroids. Other drugs (ß-blockers, thiazide diuretics) might have more subtle effects which could prove deleterious in the long term. Regular monitoring of glucose levels is advisable in subjects on long-term treatment with such agents. Drugs which cause insulin resistance could also have deleterious effects on the cardioascular risk profile, especially by increasing circulating triglyceride levels and reducing HDL cholesterol levels.

Genetic disorders

A number of rare genetic disorders (glucogen storage, familial hyperlipidemias, Friedreich's ataxia, myotonic dystrophy, Wolfram syndrome, and various insulin resistance syndromes) are associated with diabetes. There is no known treatment for these conditions and management of diabetes is along standard lines.

Summary

A relatively small proportion of diabetic patients (< 1 %) in clinical practice perhaps belong to the secondary diabetes category. Treatment of the etiological factor might "cure" diabetes in these patients and therefore, it is imperative for the treating physician to look for such factors assiduously. It now appears that even secondary diabetes tends to occur in subjets who are susceptible to develop "primary" diabetes. With better understanding of the mechanisms of action of the risk factors for primary diabetes if is possible that an increasing proportion of primary diabetes will fall in the category of secondary diabetes.

Suggested reading :

1. *Secondary Diabetes : The Spectrum of the Diabetic Syndromes.* Podolsky S, Viswanathan M, New York : eds Raven Press; 1980.

2. *Secondary Diabetes : Baillière's Clinical Endocrinology and Metabolism* (International Practice and Research). Vol 6/N° 4. Editors : Alberti KGMM, Johnston DS, eds London : Baillière Tindall; 1992.