Diabetes Mellitus in Sand Rats (*Psammomys obesus*)

Metabolic Pattern During Development of the Diabetic Syndrome

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SUMMARY

It has been reported that sand rats, naturally feeding on low-caloric-value plants containing a high concentration of salt, become obese and develop hyperglycemia when fed on a standard laboratory diet. The aim of this study was to examine the long-term effects of a synthetic-chow diet on the metabolic pattern of the diabetic syndrome in a large group of sand rats. While a few animals had a fulminant reaction with markedly decreased glucose tolerance, low plasma insulin levels, and death within 3–4 wk, most sand rats developed obesity and elevated plasma insulin levels. From the third month and forward, 40% of sand rats presented with a diabetic syndrome with hyperinsulinemia, hyperglycemia, markedly decreased glucose tolerance, and insulin resistance. This diabetic syndrome can be compared with maturity-onset (type II) diabetes. When this synthetic-chow diet was given for more than 6 mo, the majority of animals lost considerable weight and showed a major depletion of fat stores. Serum immunoreactive insulin levels fell, while blood glucose rose to above 500 mg/dl with glycosuria and ketonuria. The elevated triglyceride content of plasma and the lipid deposits in the liver were greatly augmented, and no glycogen was present. Animals developed frank insulin-dependent diabetes, and diabetic animals not treated with insulin died in diabetic coma with presumed ketoacidosis. The disease was essentially confined to sand rats showing abnormal glucose tolerance, even before eating laboratory chow. This observation suggests a genetic factor. Thus, the sand rat appears to be a potentially interesting model for investigation of both maturity-onset and insulin-dependent diabetes. **DIABETES *33*:438–443, May 1984.**

In its natural environment, the North African sand rat (*Psammomys obesus*) seems to feed exclusively on succulent plants with low caloric value and high salt content.[1,2] This animal is normally normoglycemic when eating desert vegetation, but becomes obese when allowed free access to standard laboratory chow.[3–5] Obesity, hyperinsulinemia, hyperglycemia, and, occasionally, ketoacidosis have been reported in laboratory colonies of sand rats.[6–9] While some authors claim that the sand rat provides a valuable model for investigating human diabetes,[4,7,8] others consider it to be a poor model.[10]

The present report describes a detailed characterization of the long-term effects of synthetic-chow diet on the metabolic pattern of the diabetic syndrome in a large group of Algerian sand rats.

MATERIALS AND METHODS

Animals. The sand rat (*Psammomys obesus*) is native to North Africa (Algeria). Its distribution is limited to areas where the salt content of the soil is high and the vegetation is dominated by succulent halophilic plants, primarily of the family Chenopodiaceae (*Atriplex halimus*, *Suaeda mollis*, *Salsola foetida*). This animal subsists exclusively on fresh plants whose sap has a very high salt concentration. Because of their high water content, large quantities of these plants must be ingested to achieve a sufficient caloric intake.[11]

Wild animals were trapped in the area of Beni-Abbes (30°7′ North latitude and 2°10′ West longitude) in the Algerian West Sahara and transported to Algiers. They were allowed to adapt to laboratory conditions for 15 days and fed on natural vegetables only, keeping in mind the breeding conditions previously described.[12,13] The animal room was maintained at 25 ± 2°C, relative humidity 50%, and fluorescent illumination was supplied 12 h a day. Animals were placed

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TABLE 1
Nutritional composition of experimental diets

Succulent plants of the Chenopodiaceae family (*Salsola foetida*)	
Components	Percentage of wet wt
Water	80.79
Ash	6.86
Lipids	0.40
Proteins	3.53
Carbohydrates	8.42
Total sugars	0.18
Lignin	1.12
Hemi-cellulose	2.62
Cellulose	2.23
Other (not specified)	2.27
Laboratory chow	
Components	Expressed as percentage
Water	9
Ash	7.1
Lipids	7.5
Proteins	25
Cellulose	4
Carbohydrates	47.4

in individual cages made of natural propylene 40 × 60 × 20 cm; inside, we arranged a small wooden box with an opening, mimicking their natural habitat. They were kept under continuous observation. Under these conditions, mortality was low.

One hundred and thirty-one male and female sand rats of matched ages (2–3 mo) and adapted to laboratory conditions were divided into two groups: 37 animals were fed a natural plant diet to approximate desert feeding conditions during a period of 12 mo; 94 animals were fed a laboratory-chow diet, with salt water available ad libitum during the same period. Food and water consumption were measured daily. At the time of killing, sand rats were 15 mo old.

Diet. The composition of succulent plants (*Salsola foetida*) and laboratory chow were determined by chemical analysis. It was noted that the succulent plant had a very high water content, very little total sugar, and a high proportion of salt mixture with respect to caloric substances (Table 1).

The caloric value of these plants is approximately 0.4 kcal/g wet wt, and the daily caloric intake was 20 ± 1 kcal/animal. When the sand rats were fed on laboratory chow (3.25 kcal/g), their food consumption (10 g/day) represented a higher caloric intake (32.5 ± 3 kcal/day/animal).

Specimens for analysis. Body weight was determined twice weekly. The animals were bled from the retro-orbital venous plexus weekly and blood was collected to determine plasma glucose and insulin. Glucose and ketone bodies in urine were detected with Labstix. Oral glucose tolerance tests were performed in normal, obese, and diabetic sand rats. Glucose (2 g/kg body wt) was administered orally to fasted animals overnight. Sequential blood samples were taken from the retro-orbital sinus before and 90 min after the ingestion of glucose to determine plasma glucose levels. Killing was carried out after 12 mo in normal and treated sand rats (nonfasted animals). At autopsy, the liver was removed and the adipose tissue observed.

Assays. Blood glucose was measured by the glucose-oxidase test combination (Boehringer). Plasma immunoreactive insulin (IRI) was estimated by the Phadebas insulin test. Rat insulin (Novo) was used as standard. Extraction of plasma and hepatic lipids was carried out using the method of Folch et al.[14] Total lipids were measured gravimetrically, and total and HDL cholesterol by the test combination (Boehringer). Phospholipids were determined by the method of Chen et

TABLE 2
Biochemical analysis of plasma in different groups of normal, obese, and diabetic sand rats

	Groups				
	Control (37)	Ketotic, diabetic sand rats (11)	Obese and hyperinsulinemic (49)	Diabetic and hyperinsulinemic (18)	Insulin-dependent (16)
Biochemical parameters (mg/dl)	Fed on natural vegetables	Fed on laboratory chow	Fed on laboratory chow	Fed on laboratory chow	Fed on laboratory chow
Glucose	71.5 ± 3.5 48.5 ± 4.3*	415 ± 25¶ 23 ± 4.5†,¶	81 ± 2.7§	279 ± 25¶	403 ± 30¶
Insulin (μU/ml)	42 ± 4.9 23.5 ± 3.2*	11 ± 5.5‖	267 ± 20¶	600 ± 54.5¶	22 ± 5 294 ± 45‡,¶
Phospholipids	71 ± 2.2	288 ± 9¶	72.5 ± 1.8	95 ± 6¶	293.5 ± 33¶
Total cholesterol	58 ± 3.7	386 ± 7¶	101 ± 3.5¶	158 ± 10.5¶	379 ± 28¶
Cholesterol esters	37 ± 2.5	239 ± 7¶	72 ± 2.5¶	104 ± 8¶	266 ± 19¶
Free cholesterol	21 ± 1.4	147 ± 7¶	29 ± 1.2¶	54 ± 4¶	131 ± 9¶
HDL cholesterol	41 ± 4.2		55 ± 6	56.5 ± 1.5§	40 ± 2.5
Triglycerides	72 ± 7.1	976 ± 54¶	148 ± 6¶	479 ± 56¶	1935 ± 21¶
Body wt (g)	106 ± 4.5	53.5 ± 1.8¶	121 ± 3¶	143.5 ± 7¶	89.5 ± 5.5¶

The number of animals in each group is indicated in parentheses.
*Animals after 16-h fast.
†Animals killed in premortem comatose state (three animals).
‡Insulin-treated sand rats.
The values are expressed as mean ± SEM. The degree of significance is calculated versus controls fed on natural vegetables: §$P < 0.05$, ‖$P < 0.01$, ¶$P < 0.001$.

TABLE 3
Glucose tolerance tests in normal, obese, and diabetic animals fed on different diets

Diets	Time (wk)	Initial plasma insulin (μU/ml)	Plasma glucose (mg/dl) Initial	Plasma glucose (mg/dl) 1.5-h	Abnormal tests (%)	Weight change (%)	Food intake (kcal/day)
Fresh vegetables (17)	4–24	20 ± 1.8	53 ± 4	110 ± 16	41		20 ± 1
Laboratory chow							
Hyperinsulinemic obese (32)	4–24	179 ± 10†	54 ± 1.5	154 ± 13*	71	+31	32.5 ± 2.2†
Hyperinsulinemic diabetic (8)	12–24	295 ± 19†	115 ± 16†	348 ± 44†	100	+44	32.5 ± 4.5†
After return to fresh vegetables (11)	2–4	28.5 ± 4	49 ± 3	115 ± 16	45	+3	20 ± 0.5

The number of animals in each group is indicated in parentheses. The values are expressed as mean ± SEM.
Note: "Initial" glucose (or insulin) = plasma glucose (or insulin) level before ingestion of glucose load; "1.5-h"-Glucose = plasma glucose level 1.5 h after oral administration of 2 g glucose/kg body wt. Blood glucose values were considered to be hyperglycemic (abnormal test) when they exceeded 110 mg/dl.
The degree of significance is calculated versus "fresh vegetable" group: *$P \leq 0.05$, †$P \leq 0.001$.

al.[15] The quantitative composition of the plasma and liver in terms of triglycerides, cholesterol esters, and free cholesterol was determined by thin-layer chromatography according to Landriscina et al.,[16] followed by densitometric quantification. Glycogen was extracted from liver samples in KOH at 100°C and assayed by the glucose-oxidase procedure after acid hydrolysis (HCl 1 N).

Calculations. All data were analyzed statistically with Student's *t* test and are expressed as mean ± SEM in all tables. The criterion for statistical significance was $P \leq 0.05$.

RESULTS AND DISCUSSION

Metabolic study of sand rats fed exclusively with natural plant matter. Thirty-seven adult animals fed exclusively with natural plants of the Chenopodiaceae family (directly harvested from the desert) for 12 mo served as controls. Biochemical plasma and tissue parameters were similar to those of sand rats killed in their biotope; no hyperglycemia, glycosuria, or hyperlipemia were noted (Table 2). These animals differ from controls reported in the literature, the latter being fed on fresh vegetables such as carrots, beets, and spinach.[17,18] Glucose tolerance tests were abnormal in 40% of wild animals (Table 3). This is the first report of diminished glucose tolerance in plant-fed sand rats, and suggests the existence of a genetically determined strain capable of developing diabetes after nutritional stress.

Long-term study of diabetes in sand rats fed on laboratory chow. The evolution of the diabetic syndrome in 92 male and female sand rats is described in Figure 1.

A few animals (about 15%) showed fulminant diabetes with diabetic coma and death within 3–4 wk. On the 30th day, plasma glucose values were markedly elevated (390 ± 43 mg/dl) and plasma IRI was very low; glycosuria and ketonuria were present, and there was a major decrease in body weight. Animals were killed in diabetic coma. Since urine ketones were positive, we presumed that some had ketoacidosis although plasma ketones and bicarbonate were not measured. Plasma lipids, particularly triglycerides, were greatly increased (Table 2). A large lipid accumulation in the liver was noted, and glycogen was virtually absent (Table 4). This syndrome was previously reported by Hackel et al.[19] and has features resembling severe insulin-dependent diabetes in man.

The majority of animals (about 85%) fed on laboratory chow showed a relatively large weight gain over the weeks that followed. Plasma immunoreactive insulin levels increased to 195 μU/ml on the third month of the diet; however, plasma glucose levels were not significantly altered. After the third month, there were two groups of animals, different in terms of clinical profile.

First group: as previously reported,[4,7,8] 60% of sand rats developed obesity and elevated plasma insulin levels (267 ± 12 μU/ml) during the 12-mo study. Plasma glucose values remained normal; however, small quantities of glucose were sometimes observed in the urine of some animals, suggesting that transient periods of hyperglycemia occurred but went undetected. Glucose tolerance tests become progressively more abnormal in 70% of cases (Table 3). Plasma lipids were slightly but significantly increased (Table 2), and the liver showed a moderate degree of fatty degeneration (Table 4); hepatic glycogen levels were particularly affected. Fat deposits appeared in perirenal and subcutaneous adipose tissue. In keeping with results of Hackel et al.,[20] in all animals obesity and hyperinsulinemia were readily controlled by a restriction of food rations.

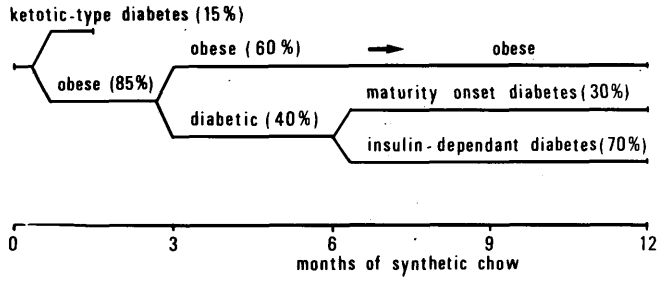

FIGURE 1. Evolution of diabetic syndrome in sand rats fed synthetic chow over 12 mo. The percentage of animals in each group is given from a pool of 92 sand rats.

TABLE 4
Biochemical analysis of liver in different groups of normal, obese, and diabetic sand rats

Biochemical parameters (mg/100 g wet wt)	Groups				
	Control (37)	Ketotic, diabetic sand rats (11)	Obese and hyperinsulinemic (49)	Diabetic and hyperinsulinemic (18)	Insulin-dependent (16)
	Fed on natural vegetables	Fed on laboratory chow	Fed on laboratory chow	Fed on laboratory chow	Fed on laboratory chow
Total lipids	3990 ± 140	5710 ± 190§	4360 ± 60§	4900 ± 190§	6170 ± 400§
Phospholipids	3230 ± 140	3260 ± 130	3190 ± 43	3130 ± 110	3410 ± 410§
Total cholesterol	273 ± 11	376 ± 7§	289 ± 7.5	322 ± 21.5†	401 ± 13.5§
Cholesterol esters	68 ± 6	132 ± 4§	90 ± 7.5†	118 ± 8.5§	198 ± 23§
Free cholesterol	205 ± 12	244 ± 4	209 ± 3.5	204 ± 14	203 ± 16
Glycerides	291 ± 19	1528 ± 62§	446 ± 24§	654 ± 79§	1892 ± 213§
Glycogen	1370 ± 497 85 ± 37*	58 ± 24	4760 ± 140§	4680 ± 240§	78 ± 31
Liver wt as % body wt	3.39 ± 0.09	5.32 ± 0.25§	3.59 ± 0.10	4.05 ± 0.12‡	6.64 ± 0.43§

The number of animals in each group is indicated in parentheses.
*Animals after 16-h fast.
The values are expressed as mean ± SEM. The degree of significance is calculated versus controls fed on natural vegetables: †$P \leq 0.05$, ‡$P \leq 0.01$, §$P \leq 0.001$.

Second group: the remaining animals (40%) developed two types of diabetic syndrome (Figure 2).

(1) Maturity-onset diabetes: There was a major increase in body weight in all animals, all of which became exceedingly obese. Blood glucose values were nearly 300 mg/dl. Glycosuria and albuminuria were strongly positive, while ketonuria was weakly positive. The renal glucose threshold is higher in sand rats than in man (2.3 g/L and 1.6 g/L, respectively). Plasma immunoreactive insulin increased continuously, reaching a peak of 600 ± 54 μU/ml. These high plasma insulin levels indicate that the primary defect is not an inability to produce insulin, but, rather, insulin resistance. Plasma lipids, in particular triglycerides, showed an increase (Table 2). In contrast with the morphologic data reported by Hackel,[17] who did not observe marked fatty changes in the liver, abundant lipid deposition was observed in the livers of our animals (Table 4). Hyperinsulinemia could be responsible for the lipid abnormalities. Indeed, it has been previously demonstrated[24] that increased insulin levels tend to increase triglyceride secretion rates. Glycogen deposition in the liver (Table 3) was high in both obese and diabetic animals, and increased with plasma IRI levels. Sand rats developed a progressive insulin resistance; continuously increasing doses of insulin were necessary to reduce hyperglycemia (Figure 2). As reported by others,[7,8,21] the in vitro sensitivity of adipose tissue to insulin decreased to a nearly complete resistance in diabetic animals. A decrease in in vitro insulin sensitivity was also found in the skeletal muscle.[22,23] Despite their high plasma IRI levels, these animals developed markedly abnormal glucose tolerance curves (Table 3), in agreement with results of Hackel et al.[19] Nevertheless, at this stage in the development of diabetes, a restricted caloric ration of laboratory chow (20 kcal versus 32.5 kcal/day/animal) decreased hyperglycemia. Return to a natural plant diet (caloric intake virtually identical to restricted caloric feeding of laboratory chow) induced a sharp decline in body weight, completely normalized blood glucose (Figure 3), and lipid metabolism returned to normal.

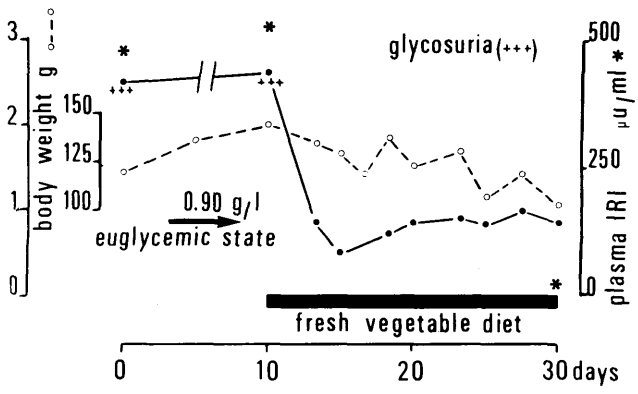

FIGURE 2. Remission of diabetic syndrome after return to natural vegetable diet. This example is particularly representative of the evolution of diabetic and hyperinsulinemic animals during restricted caloric feeding.

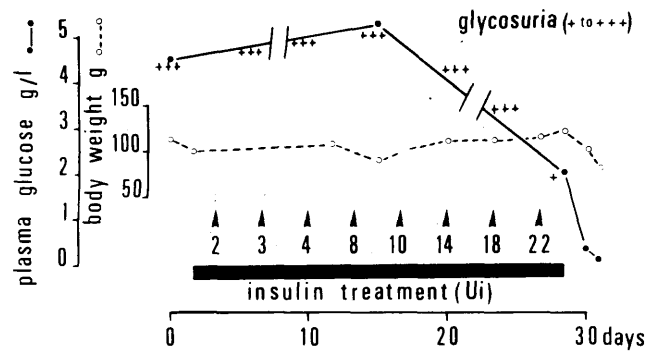

FIGURE 3. Insulin resistance in diabetic sand rats. Increasing dosage of insulin from 4 to 16 units was required to maintain normal blood glucose level.

Results for glucose tolerance tests in these animals (Table 3) were identical with controls. These results suggest that both quantitative and qualitative dietary factors play an important role. Thus, in sand rats[25] as in man,[26] weight reduction due to caloric restriction resulted in a reduction in plasma insulin levels and an improvement in glucose tolerance. The increased demand for insulin due to the abrupt change from a low- to a high-calorie diet was partially compensated for by increased pancreatic synthesis and release.[17] Despite a significant rise in plasma IRI, hyperglycemia persisted due to peripheral insulin resistance.

(2) Insulin-dependent diabetes: The second stage began after the sixth month of laboratory chow (Figure 1), when blood glucose levels reached 300–350 mg/dl plasma. Approximately 70% of animals developed a particularly severe hyperglycemia, sometimes reaching 500 mg/dl. Major glycosuria suggests that the kidney became the principal factor regulating blood glucose. High ketone levels were present in urine. Plasma immunoreactive insulin levels declined sharply (22 ± 5 U/ml), except in insulin-treated sand rats (Table 2). Body weight decreased dramatically (89.5 ± 5.5 g versus 143.5 ± 7 g in diabetic hyperinsulinemic animals), and fat stores completely disappeared. Plasma appeared lactescent, and was rich in chylomicrons. Marked hyperlipidemia was especially due to triglycerides (Table 2). Plasma triglycerides reached 1935 ± 217 mg/dl as compared with 72 ± 7 mg/dl for plant-fed animals. Marked increase in liver mass was observed. Lipid values, particularly triglycerides, were very high as a function of total hepatic mass (Table 4). To our knowledge, these lipid disorders have not previously been reported. Most of the lipids originated from the mobilization of the fat stores due to very low plasma insulin levels. Hepatic glycogen had completely disappeared. At this stage, return to a natural vegetable diet alone could no longer normalize blood glucose values, and most animals required insulin for survival. Insulin dosage varied from 4 to 16 units daily, depending upon individual sensitivity and duration of the disease. Without insulin treatment, animals died in diabetic coma with ketosis. No influence of sex was observed on the onset and the evolution of the disease. All of these manifestations are characteristic of overtly insulin-dependent diabetes, especially the latter phase of the disease. This is the first report of this particular pattern of the diabetic syndrome after 12 mo of a high-calorie diet. The long-term course of the disease renders these animals prone to microvascular complications[27] and atherosclerotic lesions.[28] Unlike results reported by Rice and Robertson,[10] we have demonstrated that the progression of the disease in a large number of obese and hyperinsulinemic sand rats leads to an insulin-dependent type of diabetes with eventual development of ketoacidosis.

The diverse sensitivity of the sand rats to the nutritional stress may be related to a genetic heterogeneity in our *Psammomys obesus*. This point is now under investigation. A protective influence of the biotope could be suggested; ultrastructural aspects of the endocrine pancreas of sand rats living in the desert were similar to those of other species,[31–34] whereas pancreatic islets from our animals presented cytologic and morphologic particularities that could account for changes in insulin secretion.[30] Likewise, water restriction led to a kidney adaptation for saving water.[35,36]

In conclusion, it appears that susceptibility to diabetes depends on the geographic origin of animals and that it is under genetic control. As suggested by preliminary data, this experimental model appears to be useful for investigation of the human disease.[27,28] Studies are in progress to evaluate incidence of the degenerative and atherosclerotic complications frequently observed in human diabetes.

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