

Chapter 15

DIABETES MELLITUS AND KLINEFELTER'S SYNDROME

PREVIOUS STUDIES OF DIABETES MELLITUS IN PATIENTS WITH KLINEFELTER'S SYNDROME

Langeron et al. (1958) described a 29-year-old patient with Klinefelter's syndrome and diabetes mellitus who developed diabetes at the age of 28 in connection with a psychogenic depression. He was started on 60 i. u. of insulin, but he later went down to 15 i. u., on which his diabetes was well regulated.

The authors mentioned that they also treated their patient with testosterone, and it was their opinion that this treatment may have had some favourable effect on his diabetes.

Castleman & Kibbee (1960) described a 49-year-old patient with Klinefelter's syndrome and no family history of diabetes who developed diabetes mellitus at the age of 19. He died at the age of 49 from late diabetic complications. *Yodaiken et al.* (1960) studied a 51-year-old patient with Klinefelter's syndrome, who developed diabetes mellitus at the age of 40 and died at the age of 54 of late diabetic complications. He had no family history of diabetes.

Autopsy showed the thyroid gland to contain an adenoma and a colloid goitre. The adrenals were markedly enlarged. The pancreas was soft but of normal appearance. The pituitary gland was microscopically normal, but it contained an excessive proportion of acidophile cells. The kidneys showed diabetic glomerulosclerosis, and there were focal areas of liver-necrosis.

The patient reported by *Yodaiken et al.* (1960) was treated with testosterone which, according to the authors, appeared to have an unfavourable effect on his diabetes. *Benda et al.* (1962) found a 41-year-old patient with Klinefelter's syndrome who developed diabetes mellitus at the age of 36. There was no further description of his diabetes. *Fraser* (1963 b) described a 71-year-old man with Klinefelter's syndrome who developed diabetes mellitus at the age of 59. His fasting insulin activity was normal but did not rise at 2½ hours after 2 grams of tolubutamide orally. Fasting blood sugar was 342 mg. per 100 ml. and urine glycosuria 2 per cent. The patient died of cardiac failure at the age of 71, and autopsy showed a normal pituitary gland, the thyroid gland was enlarged, weighing 58 grams, with nodular foci show-

ing calcifications and fibrosis. The parathyroid glands were normal. Pancreas was normal, but the Langerhans' islands showed a marked degree of hyalinization. The kidneys revealed Kimmelstiel-Wilson changes. *Rohde* (1963) described a 77-year-old patient with diabetes mellitus and Klinefelter's syndrome. There is no description of his diabetes.

Zaninovich (1964) studied a 33-year-old hypogonadal patient with chromatin-negative cells and diabetes mellitus. The patient also suffered from polycythaemia vera and high blood pressure. *Lamotte et al.* (1965) described a 41-year-old patient with Klinefelter's syndrome, insulin resistant diabetes mellitus and severe polyarthritis. He was treated with 140 i. u. of insulin, but he still had marked glycosuria. His diabetes was later fairly well regulated on 3 grams of dimethylbiguanide and 115 units of insulin. *Becker et al.* (1966) found that 5 of 50 patients with Klinefelter's syndrome had clinical diabetes mellitus. *Jackson et al.* (1966) studied the glucose metabolism in eight patients with Klinefelter's syndrome; in only two was the diagnosis made by chromosome analysis. Only one of the eight patients had a family predisposition to diabetes mellitus, as his paternal grandfather had diabetes. None of the eight patients had a diabetic glucose tolerance test. According to the authors, one patient had an early increased insulin response, and one had a delayed insulin response.

Menzinger et al. (1966) found a normal glucose tolerance test in eight patients with Klinefelter's syndrome. *Mirouze et al.* (1966 a) studied the glucose metabolism in four patients with Klinefelter's syndrome aged 49, 39, 27, and 20 years. They found diabetic glucose tolerance values in all four patients. *Wais & Salvati* (1966) found three patients with diabetes mellitus out of 32 patients with Klinefelter's syndrome (10 per cent). *Zuppinger et al.* (1967) found two patients with diabetes mellitus among 24 patients with Klinefelter's syndrome (8 per cent); there were further four patients with a diabetic glucose tolerance (16 per cent).

DIABETES MELLITUS IN PATIENTS WITH KLINEFELTER'S SYNDROME IN THE PRESENT STUDY MATERIAL AND METHODS

So far it has only been possible to make a glucose tolerance test in 10 of the 26 patients with 47,XXY, 46,XY/47,XXY and 48,XXXXY. The results of oral glucose tolerance test with determination of capillary blood-sugar by the Hagedorn-Norman Jensen method are shown in *Table 25*. The ten patients comprise three patients who previously had a glucose tolerance test made, and seven patients who were still in the hospital at the time when it was decided to make a glucose tolerance test in as many patients with

TABLE 25

Oral glucose tolerance test in 10 patients with Klinefelter's syndrome

Case No.	Age	Height in cm.	Weight in kg.	Karyotype	Glucose-tolerance test (blood-sugar in mg. per 100 ml.)						
					Fasting	1/2 hr.	1 hr.	1 1/2 hr.	2 hr.	2 1/2 hr.	3 hr.
3	43	170	64	47,XXY	84	158	121	117	102	76	75
8	39	181	56	47,XXY	74	189	184	162	149	112	84
10	30	176	87	47,XXY	76	152	196	191	175	154	128
12	37	181	63	47,XXY	87	152	101	107	80	68	70
13	46	176	58	47,XXY	82	232	214	87	63	52	58
18	20	182	107	47,XXY	82	142	127	124	112	104	—
19	71	172	72	47,XXY	73	148	222	203	178	171	89
22	14	170	90	46,XY/47,XXY	96	129	154	162	147	129	89
24	49	164	59	46,XY/47,XXY	87	148	183	142	142	101	87
26	63	170	100	48,XXXYY	114	195	237	219	162	120	110

Glucose determination was made by *Hagedorn-Norman Jensen* method.

Klinefelter's syndrome as possible. The mean age of the patients was 41.2 and the age range 43–71 with two patients above the age of 50 (*Table 25*).

RESULTS

Using the definition by *Fajans & Conn* (1959) of what constitutes a diabetic glucose tolerance test (a one-hour-value above 160 mg. per 100 ml. and a two-hour-value above 120 mg. per 100 ml.), patients Nos 8, 10, 19, 22, 24, and 26 have diabetic glucose tolerance tests (*Nielsen* (1966 a)). The number of diabetic glucose tolerance tests is, however, reduced from six to four of the ten patients, if the criteria of a diabetic glucose tolerance test are a fasting value above 100 mg. per 100 ml. or a 2 1/2-hour-value of 120 mg. per 100 ml. or above (Nos 10, 19, 22, and 26). Patient No. 10 had a mild clinical diabetes and was treated with diabetic diet.

DISCUSSION

We found that four of ten patients with Klinefelter's syndrome had a diabetic glucose tolerance with a 2 1/2-hours blood glucose value of 120 mg. per 100 ml. or above (40 per cent).

The studies of glucose tolerance in groups of patients with Klinefelter's syndrome by *Jackson et al.* (1966), *Mirouze et al.* (1966 a), *Menzinger et al.* (1966), *Zuppinger et al.* (1967), and in the present study comprise a total of 40 patients below the age of 50, 11 of whom had a diabetic glucose tolerance (28 per cent) and 14 patients aged 50+, three of whom had a diabetic glucose tolerance (25 per cent).

The present study has been extended to comprise 31 patients with Klinefelter's syndrome and more than one X in all or part of their cells by *Nielsen et al.* (1969 b); 12 of these patients had a diabetic glucose tolerance (39 per cent). The frequency of diabetic glucose tolerance was 17.4 per cent below the age of 50 and 62.5 per cent above the age of 50. This is significantly elevated, compared with the frequency found in the general population in the Birmingham Survey (1963) of 1.6 per cent with diabetic glucose tolerance for the population below the age of 50 ($P < 0.001$) and 16.1 per cent found in the population above the age of 50 ($P < 0.005$). The Birmingham Survey was chosen for comparison because it is one of the few studies which comprises an investigation of glucose tolerance in a random population sample. No expectancy rates could be calculated, as the frequency of diabetic glucose tolerance of the Birmingham Survey was only given for the population below and above the age of 50.

The frequency of overt diabetes mellitus in the 151 patients with Klinefelter's syndrome in the pooled studies by *Becker et al.* (1966), *Jackson et al.* (1966), *Mirouze et al.* (1966 a), *Menzinger et al.* (1966), *Wais & Salvati* (1966), *Zuppinger et al.* (1967), and the present study was seven per cent.

The results of the present study and the studies mentioned, indicate that there is a significantly higher frequency of diabetic glucose tolerance (chemical diabetes) in patients with Klinefelter's syndrome than expected from studies in the general population. We did not find any significantly higher frequency of overt diabetes mellitus among patients with Klinefelter's syndrome in the present study nor in the extended study by *Nielsen et al.* (1969 b). A frequency of seven per cent with overt diabetes mellitus in the pooled studies of 151 cases of this syndrome indicate, however, that there might be a comparatively high frequency also of overt diabetes mellitus among patients with Klinefelter's syndrome.

If further studies confirm the above-mentioned findings of a significantly higher frequency of chemical diabetes in patients with Klinefelter's syndrome and supernumerary X chromosome material, this would indicate that there might be a sex-linked genetic effect on glucose metabolism.

No correlation between serum growth hormone level or serum growth hormone response to an oral glucose load and the high frequency of diabetic glucose tolerance in patients with Klinefelter's syndrome was found by *Nielsen et al.* (1969 b), nor was there any correlation between urinary excretion of pituitary gonadotrophin and 17-ketosteroids on one side and the glucose tolerance on the other side.

Further studies of glucose metabolism in patients with well-defined chromosome abnormalities may increase our knowledge concerning the inheritance of diabetes mellitus, specially concerning the question whether diabetes mellitus is conditioned by autosomal or sex-linked genes.

DIABETES MELLITUS AMONG RELATIVES OF PATIENTS
WITH KLINEFELTER'S SYNDROME

The father of patient No. 5 in the present study developed diabetes mellitus at the age of 57; he had fasting blood sugar between 200 and 300 mg. per 100 ml. and from 0.4 to 1.3 per cent glycosuria. He had been treated with testosterone since the age of 32 on account of psoriasis. There is no predisposition to diabetes mellitus in his family.

The father of patient No. 22 developed diabetes mellitus at the age of 36, and he received insulin treatment from that age. He died at the age of 46 from late diabetic complications. There is a strong predisposition to diabetes mellitus in this family as seen in *Table 31*.

The mother of patient No. 7 developed diabetes mellitus at the age of 53; she was treated with insulin and diabetic diet from that age. She died from a cerebrovascular attack at the age of 65. There is no predisposition to diabetes mellitus in her family.

The mother of patient No. 16 developed diabetes mellitus at about the age of 68, but she was never treated with insulin. The cause of death at 68 is unknown. There is no predisposition to diabetes mellitus in her family.

The mother of patient No. 24 developed diabetes mellitus at the age of 38. She received insulin from that age, and she died at the age of 55 from late diabetic complications. There is a predisposition to diabetes mellitus in her family as seen in *Table 31*.

There were thus two fathers and three mothers of the 26 patients with 47,XXY or 48,XXXYY in all or part of their cells who had developed diabetes mellitus at the time of examination, four of them before the age of 60 and one at the age of 68, giving a frequency of diabetes mellitus among the parents of 9.6 per cent.

The present study has been extended to comprise 31 patients with Klinefelter's syndrome and more than one X in all or part of their cells (*Nielsen et al.* (1969 b)). Overt diabetes mellitus was found in 6 of the 39 mothers (19.4 per cent) and 2 of the 31 fathers (6.5 per cent). Fifteen of the mothers and 11 of the fathers had died at the time of the examination of their sons with Klinefelter's syndrome. Fifteen of the mothers and 12 of the fathers had not reached the age of 69 at the time of death or at the time of the examination. The mean age of the mothers at the time of death or at the time of the examination was 65 with a range from 42 to 78 years, and the mean age of the fathers was 66 with a range from 38 to 83 years.

The frequency of diabetes mellitus in the mothers (19.4 per cent) was significantly higher than the aggregated frequency of known diabetes mellitus in the Swedish female population up to the age of 69 of 8.7 per cent as found by *Grönberg et al.* (1967) ($P < 0.025$). The frequency of diabetes mellitus in the fathers of 6.5 per cent was not significantly higher than the

aggregated frequency of 4.4 per cent up to the age of 69 as found by *Grönberg et al.* (1967) in the Swedish male population. However, 12 of the fathers had not yet reached the age of 69.

Only two of the 177 siblings of the 31 patients with Klinefelter's syndrome studied by *Nielsen et al.* (1969 b) had overt diabetes mellitus, a frequency which is not higher than expected.

If further studies confirm the findings of a significantly increased frequency of diabetes mellitus among mothers of patients with Klinefelter's syndrome, this would indicate that women with diabetes mellitus might have a higher risk for non-disjunction of sex chromosomes, having children with Klinefelter's syndrome.