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Follow-up of 30 Klinefelter males treated with testosterone

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Thirty Klinefelter males treated with testosterone were studied by a follow-up examination carried out an average of 3.6 years after treatment began. The age of the men averaged 25.5 years at the time of the follow-up. Seventy-seven per cent of the men were judged to have benefited from testosterone treatment. They showed better mood, less irritability, more energy and drive, less tiredness, more endurance and strength, less need for sleep, better concentration ability and better relations with others during testosterone treatment. The beneficial effects of testosterone persisted in some of the men after cessation of treatment. The findings show that Klinefelter males given testosterone for the first time as adults can benefit from such treatment, even though it is preferable to start treatment at the age of 11-12 years.

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The present study was carried out in order to learn more about the effect of testosterone treatment in Klinefelter males. Testosterone given in adequate doses from the time of increase in follicular stimulating hormone, i.e. around the age of 11 in Klinefelter boys, may be of prophylactic value against deviations in behaviour and learning abilities. Testosterone treatment may also stimulate activity and strength and prevent fatigue in Klinefelter males. Moreover, it may increase sexual libido and potency later in life and reduce the risk of poor social relationships as well as the risk of osteoporosis and backache (Fromantin et al. 1974, Annell et al. 1970, Becker 1972, Sørensen et al. 1981, Nielsen & Sørensen 1984).

In the present study, 30 adult males with Klinefelter's syndrome were examined after varying lengths of treatment with testosterone, in order to determine whether the treatment had had beneficial effects.

Material and Methods

All Klinefelter males who were given testosterone treatment in our laboratory during the years l970-l982 were studied. Two Klinefelter males previously treated with testosterone were, however, excluded from the study because we were unable to contact them at the time of the follow-up. Thus, 30 Klinefelter males were included in the present study. Information was obtained by telephone interview with the males, with their parents, and with their general practitioners. In addition, case histories were examined in those subjects who had been hospitalized during the follow-up period.

The testosterone preparations used were either: Testoviron^{R} depot (1 ml containing testosterone enantate 110 mg) or testosterone proprionate (25 mg) or Restandol^{R} one tablet containing testosterone undecanoate (40 mg).

Results

The age distribution of the males appears in Table 1, the ascertainment in Table 2, and their occupations at the time of the follow-up examination in Table 3. The average duration of testosterone treatment was 3.6 + 3.1 years in the males. The overall evaluation indicated that testosterone treatment had a good effect in 23 of the males (77%), whereas a moderate effect was noted in 2 of them (7%). No effect of testosterone treatment was obtained in 5 males (17 %). Table 4 shows the effect of testosterone treatment on the physical and/or mental condition of the males.

Improvement during testosterone treatment was characterized mainly by more endurance and strength, less fatigue, less

need for sleep, more activity, enhanced drive, better working capacity, improved concentration, better learning ability, better mood, less irritability, and better relations with others.

There was a significantly higher frequency of unskilled labourers than of skilled labourers among those who had discontinued testosterone treatment at the time of the follow-up. The frequency of socially well-adjusted individuals was higher among the Klinefelter males who had continued testosterone treatment (86%) than

Table 1

Age distribution at first contact and at present examination

Age distribution	First contact	Present examination
10 - 14	8	-
15 - 19	15	5
20 - 24	3	12
25 - 29	1	5
30 - 34	2	3
35 - 39	1	3
40 - 44	-	2
Total	30	30

Table 2

Distribution by ascertainment

Ascertainment	Total
Schoolboy study	13
Referred by general pracitioners	7
Referred from psychiatric hospitals	5
Referred from paediatric, medical and surgical departments	5
Total	30

among those who had discontinued treatment (76%), although that difference was not significant (Fischer test, p = 0.086). Several of those who had discontinued treatment experienced a setback to pretreatment conditions, whereas improvements

usually occurred after testosterone treatment was started again. In some cases, however, where definite improvements occurred during 1-2 years of testosterone treatment, the improvement continued after cessation of treatment.

The following brief case reports describe some of the findings in the males, typical of the results of testosterone treatment.

No.1 at the Age of 20

This man was from the schoolboy study. His karyotype is 47,XXY. He received 160 mg testosterone undecanoate daily from age 17 to 19 years. He reported that his mood had improved and that he concentrated better on school work during testosterone

Table 3

Occupational status and employment

Occupational status	Total	%
Skilled labourer	6	20
Unskilled labourer	15	50
Apprentice/student	5	17
Disablement pensioner	4	13
Total	30	100

Only 3 were unemployed.

treatment. His teachers reported that he seemed to be happier, that he took the initiative more often in his relations with schoolmates and that he concentrated better on his school work. When testosterone treatment was stopped for a short period, he again became passive, fatigued, and showed a decreased level of concentration. Therefore, he resumed testosterone treatment. He finished school at the age of 20 with satisfactory grades. He spent half a year at a folk high school, and at the time of the follow-up he was working in a factory learning to use a knitting machine. His mother reported that he did well when he recieved testosterone treatment, but if he stopped taking the hormone, he became irritable, aggressive and hot-tempered. He was receiving 240 mg testosterone undecanoate daily at the time of the follow-up. The effect of testosterone treatment in this man was rated as good.

No.6 at the Age of 23

This man was from the schoolboy study. His karyo type was 47,XXY. He received testosterone from age 17 to 18 years. He reported that his mood and physical strength improved during hormone treatment. His parents said that he appeared less nervous during testosterone treatment. However, when he stopped taking testosterone, he had more problems with his school work. He started to take testosterone again and obtained a good response.

Table 4

Effect of testosterone treatment on physical and/or mental conditions

Effect	Total	%
Good	23	77
Some	2	7
None	5	17

Total	30	101

At the time of the follow-up (age 23 years), he was receiving 135 mg testosterone as depot-injection every 3 weeks. The effect of testosterone in this male was rated as good.

No. 9 at the Age of 22

This man was from the schoolboy study. His karyotype was 47,XXY. He received 135 mg testosterone by depot-injection once a month for 1 year at the age 17 to 18. He did not feel that the treatment had an effect, and thus stopped taking it. He was not receiving treatment with testosterone at the time of the follow-up (age 22). He was irritable and had difficulties managing his job. He reported at the follow-up that he had felt better while taking testosterone, and he agreed to resume treatment. He was tired and had difficulties getting up in the morning. He was trained as a cook, but was working as an unskilled factory worker. He had applied to become a soldier at the time of the follow-up. Testosterone treatment was rated as having no effect in this man.

No. 11 at the Age of 23

This man with karyotype 47,XXY was from the schoolboy study. He had received 135 mg testosterone by depot-injection every 3 weeks from the age of 18 to 20 years. He felt better on testosterone treatment, and his mother said that he had become more outgoing and had more friends. His teachers said that he was more attentive and concentrated better in school and that he got better grades after testosterone treatment was begun. At the age of 23, he had not received testosterone for 3 years, but he still felt fine. He had a good job as a mechanic, good friends, and was healthy, physically and mentally. The effect of testosterone treatment in this man was rated as good.

Table 5

Occupational status in relation to testosterone treatment

	Testosterone treatment at present		Previous testosterone treatment, but not at present	
Occupational Status	Total	%	Total	%
Skilled labourer	5	36	1	6*
Unskilled labourer	5	36	10	62
Apprentice/student	2	14	3	19
Disablement pensioner	2	14	2	13

**P (Fisher)=0.054.*

No. 12 at the Age of 23

This 23-year-old man with karyotype 47,XXY was from the schoolboy study. He received 135 mg testosterone by depot-injection every 3 weeks for 2 years, from age 18. He stopped taking testosterone for a while, but became more fatigued. Therefore, he started treatment again. His mother reported that he had been more active and happy during testosterone treatment, and his teachers confirmed that. At the age of 23 he was still being treated with testosterone, receiving 160 mg testosterone undecanoate daily. He was healthy, socially well-adjusted, and had a job as a farmer. The effect of testosterone treatment was rated as good.

Table 6

Social adjustment in relation to testosterone treatment

	Testosterone treatment		Previous testosterone treatment, but not at present	
Social adjustment	Total	%	Total	%
Well adjusted	12	86	9	56
Unsatisfactory adjustment	2	14	7	44
Total	14	100	16	100

The differences are not statistically significant.

No. 13 at the Age of 23

This man with karyotype 47,XXY was from the schoolboy study. He had been treated with 135 mg testosterone by depot-injection every 3 weeks for 3 years, starting at the age of 18. His teachers reported that his aggressive and destructive tendencies, which were present before treatment, abated during hormone treatment, and that he did much better at school. He finished school with good grades. He was an active sportsman participating in national competitions. However, he considered testosterone treatment to be taking dope, so he stopped taking it. He then became much more fatigued, irritable, and had difficulties coping with his work. Nevertheless, he did not want to resume treatment with testosterone, even though the medical committee of the Danish National League of Sports decided that testosterone treatment for Klinefelter's syndrome is not taking dope. At the age of 23, he was satisfied working as a truck driver. He was still active in his favourite sport, and taught it to young people. He did not take testosterone at the time of the follow up. The effect of testosterone treatment in this man was rated as good.

No. 14 at the Age of 23

This man with karyotype 47,XXY was from the schoolboy study. At the age of 18, he received a testosterone injection (135 mg depot) every 3 weeks. He reported at the follow-up that he had stopped the treatment after a few months, and that he did not remember whether it had any real effect. He had been unemployed for a long time, but at the follow-up he was doing a 7-month period of work for long-term unemployed. He was very tired and had to go to bed immediately when he came home from work. Testosterone treatment was rated as having no effect.

No. 17 at the Age of 41

This man with karyotype 47,XXY was referred from a psychiatric hospital. Treatment with testosterone (135 mg depot) every 3 weeks was started at the age of 33. Treatment was stopped after approximately a year, for unknown reasons. During treatment, the patient, who was quite inactive and passive, with psychotic traits, became more active and had more energy, but his psychotic symptoms remained. At the follow-up, he was in a nursing home and was being treated for a paranoid psychosis of uncertain type. Testosterone treatment was rated as having a moderate effect.

No. 18 at the Age of 28

This man with karyotype 47,XXY was referred by his general practitioner at age 24. Treatment with testosterone undecanoate (120 mg daily) began at age 24. The treatment was later changed to depot- injection (135 mg) every 4 weeks. The patient was border-line mentally retarded. He became much less tired, more active and in a better mood during treatment. Previously, he had a strong urge to commit minor criminal acts. That urge was, however, much reduced during testosterone treatment. The effect of testosterone treatment was rated as good.

No. 19 at the Age of 29

This man with karyotype 47,XXY was referred by his general practitioner at the age of 21. Testosterone treatment was started at the age of 2l with a depot-injection (135 mg) every 3 weeks. He was later changed to daily treatment with testosterone undecanoate (120 mg). At the follow-up, he was receiving a depot-injection (135 mg) every 2 weeks. Before treatment, this patient had fits of rage, abused alcohol, and had periods of dysphoria. During treatment, he had no fits of rage, and hardly any periods of dysphoria or alcohol abuse. At the follow-up, he was living with a girlfriend and had a normal sexual life. He has a disability pension but also works as a gardener for 6 h daily. The effect of testosterone treatment was rated as good.

No. 20 at the Age of 27

This man with karyotype 47,XXY was referred from an institute for the mentally retarded at the age of 17. He received testosterone (135 mg depot) every third week for 8 years. During treatment he had better mood, better concentration, better social adjustment and better contact with others. At the follow-up, he was living alone, but had his meals with his parents. He took care of their garden and kept busy with different types of hobbies. The effect of testosterone treatment was rated as good.

No.27 at the Age of 18

This man with karyotype 47,XXY was referred from a neurological department at the age of 15. He had received testosterone undecanoate daily (120 mg) for the past 3 years. His mother reported that the treatment had good effects, in that he was less tired, stronger and more stable at work. However, he said that the treatment had not helped him much. He was working in a factory where he had been for the past 3 years. He enjoyed his work and had good relations with others. Testosterone treatment was rated as having some effect.

No. 29 at the Age of 27

This man with karyotype 47,XXY was referred from a child psychiatric hospital at the age of 10. He received testosterone (135 mg depot) every 3 weeks from the age of 17. During testosterone treatment, he became more active and less tired. His behaviour improved and he did better at school. When he occasionally stopped taking testosterone, he became tired, passive, and was on the border-line of mental illness. He had been working for the last 7½ years at the time of the

follow-up, and was doing well at his job. The effect of testosterone was rated as good.

No. 30 at the Age of 41

This man with karyotype 47,XXY asked for treatment at the age of 36. He had received 160 mg testosterone undecanoate since then (5 years). His condition improved during treatment. He was less tired, more independent and had more initiative. His tendency to obesity disappeared. He had more beard growth and his sexual life had improved. He had a rather demanding job that he managed successfully. The effect of testosterone treatment was rated as good.

No. 32 at the Age of 35

This man with karyotype 47,XXY was found in an epidemiological study of Klinefelter males among conscripts. He was treated with testosterone (135 mg depot) every 3 weeks from the age of 20 to the age of 30. Since then, he had received daily treatment with testosterone undecanoate (120 mg). During treatment with testosterone, he became less shy and his self-confidence improved. He developed normal body hair growth and his sexual potency improved. His concentration and memory improved and his mood became more stable. He improved to the extent that he did not need the disability pension which he had received for several years due to tiredness and backache. He had a good job at the follow-up. The effect of testosterone treatment was rated as good.

No. 35 at the Age of 31

This man with karyotype 47,XXY was referred from a psychiatric hospital. He was treated with testosterone for 1 year from the age of 28. During that time, his mood improved and became more stable. His previous alcohol abuse disappeared and he became less tired. However, he stopped taking testosterone because he felt well. Since then, he has had periods of dysphoria, tiredness, instability in his work and alcohol abuse. The effect of testosterone treatment was rated as good.

No. 36 at the Age of 31

This man with karyotype 46,XY/47,XXY was referred from a neurological department. He began testosterone treatment at the age of 16. Previous to treatment, he was easily fatigued, often had headache and lacked appetite. After testosterone treatment was begun, he became less tired, his headaches disappeared and his appetite increased. He became more active and his ability to concentrate improved. He received a disability pension at a time ~hen he had psychological problems. At the follow-up, he was receiving testosterone (135 mg depot) every 2 weeks. He was active, had many spare-time interests, had good friends, lived with a girlfriend and was socially well adjusted. The effect of testosterone treatment was rated as good.

Discussion

Double-blind studies of testosterone treatment in unselected groups of males with KIinefelter's syndrome would be the ideal way of studying the effect of such treatment. Sufficiently large, unselected groups of Klinefelter males are, however, unavailable for such studies. In the present study, a follow-up examination was carried out in a relatively large group of Klinefelter males who had received testosterone treatment for some time. The present findings indicate that the majority (77%) of these men benefited from testosterone treatment. It is noteworthy that some of the subjects who benefited from treatment began it after the age of 18, in accordance with some previous reports (Bablock & Janczewski 1969, Annell et al. 1970, Myhre et al. 1970, Becker 1972, Fromantin et al. 1974).

Stewart et al. (1986) found no significant effect of testosterone treatment in 9 Klinefelter-boys compared with 12 controls from age 13 to 15. Behaviour results were, however, only reported from age 13 to 14 years, and testosterone was only

given in doses of 100 mg testosterone cypionate intramuscularly every 4 weeks. The authors stress that treatment with higher and more physiological doses given at more frequent intervals might produce beneficial effects on psycho-social adaptation and psycho-social adjustment in Klinefelter boys. Testosterone cypionate and testosterone enantate induce an increase in the serum testosterone level for only 12 to 14 days. Intervals of 4 weeks between injections, as used by Stewart et al. (1986), are thus too long, and the lack of any significant effect of testosterone treatment as found by Stewart et al. cannot be taken as evidence of lack of effect of testosterone treatment.

The best time to start testosterone treatment is around the age of 11-12 years, when marked rises in FSH and HGH concentrations occur. According to our experience, the best type of treatment is testosterone undecanoate given orally at meal times. Testosterone given in that way is absorbed directly into the lymph from the gut. For long-term substitute treatment, 40 mg of testosterone undecanoate given 3 times daily is required (Skakkebæk et al. 1981). The short-lived serum testosterone peaks resulting from administration of testosterone undecanoate enable the testes to resume their own steroid biosynthesis (Nieschlag 1984). Thus, testosterone undecanoate offers the advantage of unsuppressed testicular androgen production in intervals between testosterone serum peaks. We have, however, also seen beneficial effects of testosterone given by depot injection. Furthermore, some males prefer depot treatment with testosterone every 2-3 weeks rather than taking testosterone tablets at meals three times daily.

Cessation of testosterone treatment in the subjects in the present study who had improved during treatment resulted in relapse to pretreatment conditions. We found, however, that in a few cases the improvement obtained during testosterone treatment continued after cessation of treatment. Improvement during long-term testosterone treatment, combined with a positive reaction to this improvement from the surroundings, may have prevented relapse after cessation of treatment in a few cases.

There was a higher frequency of skilled than unskilled workers among those who had continued testosterone treatment, and there was a tendency for Klinefelter males who had continued treatment to be better socially adjusted than those who did not. It is noteworthy that only 10% of the subjects were unemployed at the follow-up, and that the majority of the subjects (88%) were well adjusted socially as far as work is concerned. We believe that one of the beneficial effects of testosterone treatment was generally to improve the ability of the Klinefelter males at work.

The four Klinefelter males who were in receipt of a disablement pension did not get it for the Klinefelter syndrome alone. One of them, who had been followed in our laboratory for about 12 years, had a very stressful childhood with a mother who suffered from hysterical neurosis and was extremely overprotecting and demanding. The parents were divorced, and the mother developed alcohol abuse. At present, at the age of 3l, he is doing very well on testosterone treatment. He is active and has many interests. He has a girl friend and a good quality of life. Another of the four males who has a disablement pension also had a very stressful childhood with a stepfather who did not like him. He developed epilepsy with grand mal fits and a paranoid psychosis, and is at present in a nursing home. The third Klinefelter male with a disablement pension is mentally retarded and partly because of this he has had difficulties in keeping a job. He is, however, doing quite well after being started on testosterone treatment. The fourth patient who receives a disablement pension also grew up in a home with many problems. He suffered from fits of rage, and during periods of dysphoria he developed alcohol abuse. He is at present being treated with testosterone, and he is doing well. He has no alcohol abuse, no fits of rage and hardly any dysphoric periods. He lives with his girl friend, and in spite of getting a disablement pension he has a job as a gardener and is socially well adjusted.

The diagnosis of Klinefelter's syndrome is often first made in adults. It would, however, be of value to diagnose Klinefelter's syndrome as early as possible, for example by measuring the size of testes in all schoolboys at the age of 11-15 years and by carrying out chromosome examinations in boys with testes below 2 ml. Such screening methods could be carried out readily as a part of prophylactic examination procedures by school physicians in most countries. We recommend that treatment with testosterone undecanoate (Restandol) is offered to all boys with Klinefelter's syndrome, preferably at the age of 11-12 years. If, however, the diagnoses of Klinefelter's syndrome are first made after puberty, our findings indicate that testosterone treatment can still have beneficial effects. In fact, we have observed beneficial effects of testosterone treatment in 20-30-year-old Klinefelter males receiving the hormone for the first time.

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