Journal of Medicinal and Chemical Sciences 6 (2023) 2531-2538

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Original Article

Effect of Androgen Use among Children with Micropenis in Erbil City

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ARTICLE INFO

Article history

Receive: 2023-03-08
Received in revised: 2023-04-23
Accepted: 2023-05-24
Manuscript ID: JMCS-2305-2057
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatima Ramezani
Editor who approved publication:
Dr. Majid Hajifaraji

DOI:10.26655/JMCHEMSCI.2023.10.27

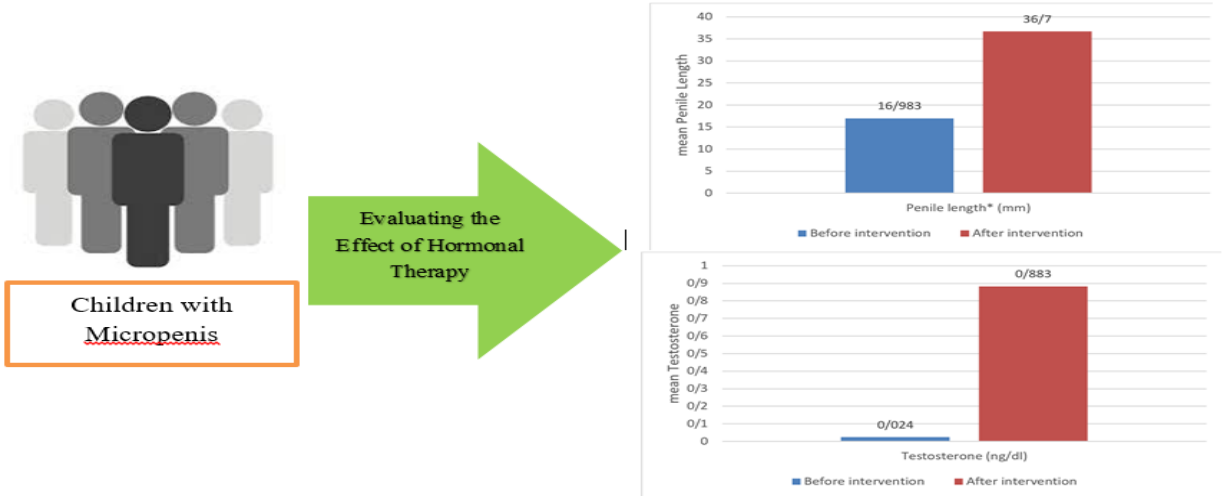
KEYWORDS

Androgen
Child
Hormone
Sustanon

ABSTRACT

Background and objective: Micropenis is a condition where the penis is smaller than average, causing psychological distress and affecting sexual function. The aim of this study was to determine the effect of androgen therapy on gonadal response and penis growth in children with micropenis.
Method: This was a retrospective and prospective study including a sample of 30 children in the age range of 9-13 years old with micropenis from March 2019 to December 2022 in Erbil, Iraq. Informed consent was obtained from the legal guardian of the children. Demographic information, drug dosage, testosterone level, and penis length were collected and recorded before and after the therapeutic intervention. All participants received a therapeutic regimen involving Sustanon 250 mg/1ml injections.
Result: In this study, the age of the patients participating in the study was between 9 and13 with an average (standard deviation) of 11.176 ± 0.567 years old. The number of treatment doses varied, with 16.7% receiving one dose, 33.3% receiving two doses, and 50% receiving three doses. Testosterone levels significantly increased from a mean of 0.024 ± 0.007 ng/dl before the intervention to 0.883 ± 0.318 ng/dl after ($p \leq 0.001$). In addition, penile length significantly increased from a mean of 16.983 ± 1.923 mm before the intervention to 36.7 ± 3.485 mm after ($p \leq 0.001$).
Conclusion; Androgen can be useful in the treatment of micropenis because the results showed that it increased both the testosterone level and the penis length.

GRAPHICAL ABSTRACT



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Introduction

Male testosterone production is essential for a broad variety of functions. Exposure to testosterone has a significant impact on the development of external and internal genitalia, secondary sexual traits, spermatogenesis, growth rate, bone mass density, psychological puberty, and metabolic and cardiovascular profiles [1]. The formation and growth of penile are an androgen-dependent process. Disruption of this androgen signalling system can result in attenuated penile development, also known as micropenis, which affects up to 0.7% of newborn boys [2]. Micropenis is diagnosed when a patient's penile length is less than -2.5 standard deviations from the mean without hypospadias. For an infant of 0 to 5 months old, the lower limit is 1.9 cm. A pragmatic approach would be to evaluate all boys with a stretched penile length below 2 cm, as congenital micropenis can be a marker for a wide range of endocrine conditions. It is estimated that worldwide, micropenis affects 1.5 out of every 10,000 male babies [3-5].

Micropenis, typically diagnosed during infancy or early childhood, can stem from various causes. A significant factor is the occurrence of hormonal imbalances during fetal development or early stages of childhood. Inadequate production or impaired functioning of testosterone, the primary male sex hormone, can lead to insufficient penile growth. Micropenis can also be linked to genetic disorders, such as Klinefelter syndrome or certain intersex conditions. Prenatal exposure to specific medications, like anti-androgens, or exposure to chemicals that disrupt the endocrine system can interfere with normal penile development. Moreover, hormonal disorders, chromosomal abnormalities, and underlying medical conditions affecting the endocrine system can contribute to the micropenis development [5-7].

The psychological impact of micropenis can be significant, with affected individuals often experiencing shame, embarrassment, and anxiety about their appearance and sexual function. Therefore, prompt and appropriate treatment is essential to improve the patient's quality of life [8].

Treatment options for micropenis vary, and the use of androgens, such as testosterone, has been a subject of interest and controversy in the medical community [6]. Childhood and puberty are among the life phases in which androgen production disorders can manifest and testosterone therapy (TT) is frequently the only remedy that can treat the underlying deficiency [1].

Studies have shown that testosterone therapy can stimulate penile growth and improve stretched penile length (SPL) in individuals with micropenis [9]. The results of Xu *et al.*'s study (2017) showed that androgen therapy is beneficial for micropenis. In their study, they found that the short-term and topical use of dihydrotestosterone (DHT) in low doses in patients with micropenis can accelerate penile growth effectively without obvious side effects [10]. The results of Nerli *et al.*'s study (2013), showed that the exogenous administration of testosterone to pre-puberty boys and human chorionic androgen (hCG) to pubertal or post-puberty boys leads to a significant increase in penis length [11].

Due to the influence of genetics, ethnicity, and the limited research conducted in Iraq, a study was essential in Erbil to examine how androgen therapy impacts gonadal response and penis growth in children with micropenis.

Materials and Methods

Study design

For this study on the effect of androgen use among children with micropenis, a comprehensive approach was employed to ensure transparency in the sampling process. It was conducted as a combination of retrospective and prospective methods at two clinics: a private clinic and the outpatient clinic at Rapareen Children's Teaching Hospital in Erbil, Iraq. The study included all children who were diagnosed with micropenis from March 2019 to December 2022.

The aim of this study was to determine the effect of androgen therapy on gonadal response and penis growth in children with micropenis.

Participants

A total of 30 children entered the study. Information about the age, weight, and medical history of the participants was collected. The medical history included any known conditions or treatments that could cause micropenises, such as hormone imbalances, genetic disorders, or exposure to certain medications.

Information about the age, weight, dose of medication received, testosterone level, and penis length before and after the therapeutic intervention was also recorded.

Inclusion criteria included all males between 9 and 13 years old near puberty age group, diagnosed with micropenis, with a penile length less than 2.5 standard deviations below the mean (less than 2 cm), and parental consent to participate in the study.

Participants were excluded from the study if their parents withdrew consent, if they had other genital abnormalities like hypospadias, if they experienced intolerable side effects from androgen use, if they had contraindications to androgen therapy, or if they did not complete full course of treatment.

Intervention

The study employed a standardized methodology to ensure accurate data collection. Initially, eligible children meeting the inclusion criteria underwent thorough examinations by a collaborating specialist. To account for the fatty tissue in the pubic area, penile length measurements were taken from the top of the pubis using a ruler, ensuring the hidden portion of the penis was not overlooked.

Following each hormone therapy session, blood samples were collected from the children and sent to the laboratory for serum testosterone level testing. The obtained results were meticulously documented. The study included participants who received a therapeutic regimen involving Sustanon 250 mg/1 ml injections. These injections consisted of a combination of testosterone propionate (30 mg/ml), testosterone phenylpropionate (60 mg/ml), testosterone isocaproate (60 mg/ml), and testosterone decanoate (100 mg/ml). The injections were administered deep into the muscle on a monthly basis for a duration of 1, 2, or 3 months, depending on the prescribed treatment plan. After the treatment period, measurements of penile size and testosterone plasma levels were taken, and the obtained data were carefully recorded for the subsequent analysis.

Blinding methods were employed to minimize biases and maintain the integrity of the study. Data collectors, outcome assessors, and data analysts were kept unaware of the specific treatment given to each participant through anonymized coding or identification numbers. This helped reduce the potential for bias and ensured the validity and reliability of the study's results.

Data analysis

The Statistical Package for the Social Sciences (SPSS) version 26 software was employed for data entry and analysis, ensuring accuracy, and reliability. Descriptive statistics, including measures such as mean, standard deviation (SD), and frequencies, were used to summarize the characteristics of the participants, including their age, weight, medical history, the dose of medication received, testosterone level, and penile length before and after the therapeutic intervention. To assess the significance of the treatment, paired t-tests were conducted to compare the mean penile size and testosterone levels before and after the intervention. The significance level was set at $p < 0.05$ to determine the statistical significance of the findings.

Ethical considerations

Informed consent was obtained from the parents or legal guardians of the participants. The privacy and confidentiality of the participants were ensured by maintaining anonymity and using secure data storage. Also, in this study, the Declaration of Helsinki was followed to comply with ethical principles.

Results and Discussion

The study participants had a mean age of 11.176 ± 0.567 CI95%: 10.96–11.38 years old, indicating

a narrow age range within the sample. The average weight of the patients was 47.506 ± 8.139 CI95%: 44.467 – 50.545 kg, showing variation in the weight distribution. Baseline testosterone levels were measured with a mean of 0.024 ± 0.007, CI95%: 0.021–0.027 (ng/dl), providing insights into the initial hormone status. The mean penile length was recorded as 16.983 ± 1.923 CI95%: 16.265-17.701 mm, reflecting the starting point for evaluating the growth.

The examination of the number of drug doses revealed that 5 (16.7%) participants received one treatment dose, 10 (33.3%) received two treatment doses, and 15 (50%) received three treatment doses (Table 1), indicating varying treatment regimens among the participants.

The findings from investigating the variable of family history of micropenis among the subjects revealed that 43.3% (13 individuals) had a positive family history of micropenis, while 56.7% (17 individuals) had no reported family history (Figure 1).

Testosterone variable results showed that the mean before the intervention was 0.024 ± 0.007 ng/dl and the mean after the intervention was 0.883 ± 0.318 ng/dl, the mean difference of testosterone was equal to 0.859 ± (1.24) ng/dl. ($p \leq 0.001$), which shows the significant effect of androgen on increasing the mean testosterone.

The results of the penile length variable investigation showed that the mean before the intervention was 16.983 ± 1.923 mm and the mean after the intervention was 16.983 ± 1.923 mm.

Table 1: The basal characteristics of the patients before Androgen treatment

Variable		Mean ± SD, CI:95%
Number of patients		30
Age (year)		11.176 ± 0.567, 10.96 – 11.38
Weight (kg)		47.506 ± 8.139, 44.467 – 50.545
Testosterone (ng/dl)		0.024 ± 0.007, 0.021 – 0.027
Penile length* (mm)		16.983 ± 1.923, 16.265 – 17.701
Number of doses	1	5 (16.7%)*
	2	10 (33.3%)*
	3	15 (50%)*

SD: standard deviation, Frequency (%).*

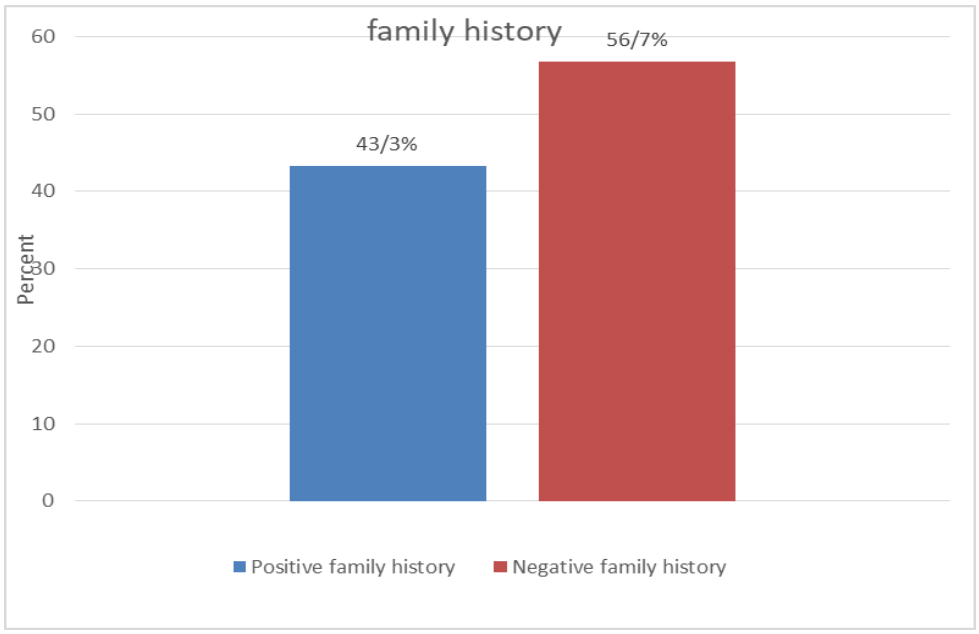

Figure 1: Family history of the micro penis in children

Table 2: Testosterone levels and penile length volume before and after human androgen treatment

Variable	Before intervention mean±SD	After intervention mean±SD	Mean difference	P-value*
Testosterone (ng/dl)	0.024 ± 0.007	0.883 ± 0.318	0.859 ± (1.24)	0.001
Penile length (mm)	16.983 ± 1.923	36.7 ± 3.485	19.717 ± (2.25)	0.001

** P-value; Paired t-test.*

The mean difference of penile length was equal to 19.717 ± (2.25) ($p \leq 0.001$), which shows the significant effect of androgen on increasing the penile length (Table 2). The mean before and after the testosterone intervention as well as the significant effect of androgen on the mean increase in testosterone are depicted in Figure 2. In addition, Figure 3 demonstrates the mean before and after the intervention of penile length and the significant effect of androgen on increasing penile length.

In this study, the effect of androgen hormone on increasing penile length was investigated. Based on the results, it was shown that androgen hormone was able to increase testosterone level and penis length in micropenis patients.

Exposure to environmental factors of androgens, anti-androgens, and substances that disrupt the endocrine system during the fetal period can cause a disruption in the function of hormones and tissue response and lead to an abnormal sexual phenotype; these abnormalities can cause the shape and size of the external reproductive system to be disturbed [12, 13].

Micropenis can be the only disorder caused by the hypothalamus-pituitary axis, which is associated with the deficiency of several pituitary hormones. Hypoglycemia, growth hormone deficiency, thyroid disorders, and impotence can be mentioned among the dangers of this hypothalamus-pituitary axis. Therefore, it is necessary to evaluate and measure the length of penis in male infants to diagnose micropenis and perform diagnostic and therapeutic work [14, 15].

Nerli *et al.* (2013) conducted a study in India with the aim of determining the effect of androgen hormone on penis growth in micropenis children. In Nerli's study, children were affected by androgen hormone. The results of this study, which are in line with the results of the present study, showed that the androgen hormone had a direct and positive effect on increasing the length of penis and can be used as a standard treatment protocol in children [11].

Due to the lack of systematic studies to compare the effect of different treatment options on long-term outcomes, in terms of genital appearance, quality of life, and sexual satisfaction in children with micropenis, a systematic review was conducted by Stancampiano *et al.* (2022). Stancampiano *et al.* examined different treatment approaches and found compelling evidence supporting the effectiveness of androgen therapy in treating micropenis. The results of this study align with the current findings, demonstrating that the use of androgens can lead to highly positive outcomes in the micropenistreatment [5].

Kim *et al.* (2011) conducted a study to investigate the effect of androgen treatment on the response of gonads and penis growth in children with micropenis. Twenty patients who met the criteria for micropenis were included in the study. In this study, androgen hormone (1500-2000 IU) was administered intramuscularly 3 times a week for 8 weeks, and the results showed that testosterone level increased significantly after androgen hormone administration. Likewise, the mean length of penis increased significantly 24 weeks after the start of treatment, which shows the importance of the results of the present study, which can ensure the recovery of patients if androgen hormone is used [16].

In case of dissatisfaction with the initial treatment with androgen, the hormone can be re-administered in a short period of time to increase the size of penis, and the patient receives the appropriate treatment response [17].

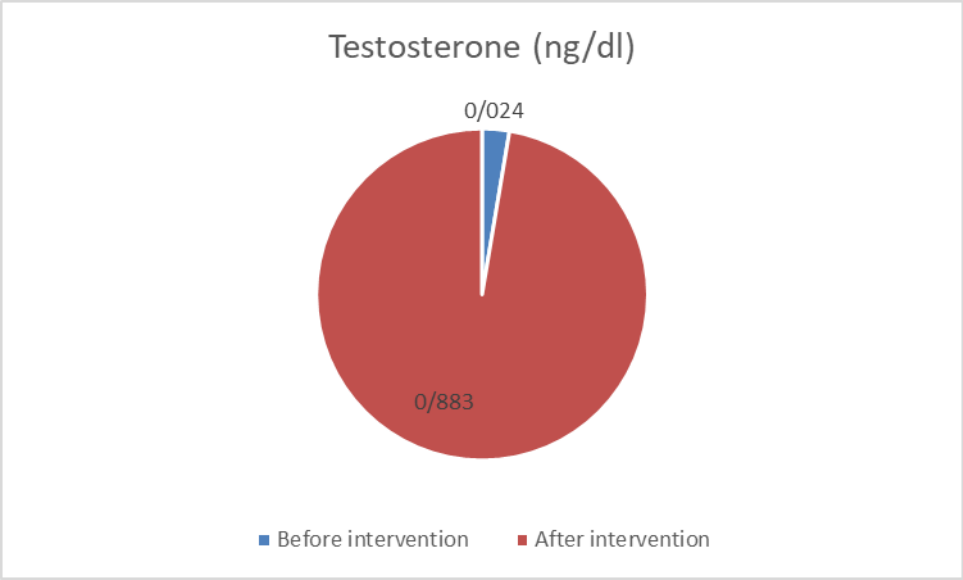

Figure 2: Mean testosterone before and after the intervention

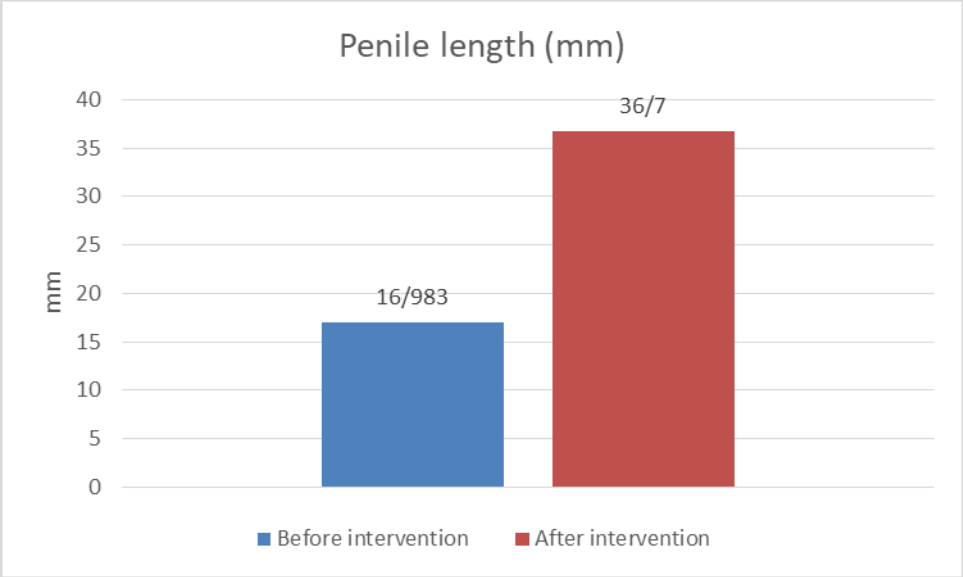

Figure 3: Mean penile length before and after the intervention

It has also been shown that the use of hormones in the treatment of micropenis is not associated with treatment failure in the long term and after puberty [18, 19].

Penis length during childhood and puberty is strongly influenced by androgen and testosterone hormones and to a lesser extent by growth hormones, accordingly, this study showed that treatment with androgen and testosterone hormones in childhood led to a sufficient increase in penis size. In summary, micropenis is a medical emergency that can be different from many other abnormalities and syndromes. Concerning the causes of micropenis, endocrine evaluation can help to determine the cause and treatment of micropenis, and it should be noted that early diagnosis is important for various treatment options.

Conclusion

The findings of this study had significant implications for the clinical management of micropenis in children. The effectiveness of androgen therapy in increasing testosterone levels and penile length highlights its potential as a valuable treatment option, addressing both hormonal imbalances and physical growth. These results underscore the importance of further

research to investigate long-term effects, determine optimal dosage and duration, and assess the psychological impact of androgen therapy. Ultimately, these findings contribute to enhance clinical practice, guide treatment decisions, and shape future research directions in the field of micropenis treatment.

Acknowledgements The authors would like to express their sincere thanks to all those who have helped in the completion of this research project, children, parents, medical staff, colleagues, and academic institution staff who have been effective in the success of this study. Their support, cooperation, and help have been valuable, and the authors sincerely thank them for their help.

Limitation

The study was conducted in a single geographic location, which may limit the findings generalizability. In addition, the study may have been subject to selection bias, as it only included children who sought medical attention for micropenis. Finally, the study was limited by the availability of medical records, which may have varied in completeness and quality.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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HOW TO CITE THIS ARTICLE
Wesam Amjad Boya Kaka, Effect of Androgen Use among Children with Micropenis in Erbil City. *J. Med. Chem. Sci*., 2023, 6(10) 2531-2538
DOI: https://doi.org/10.26655/JMCHEMSCI.2023.10.27
URL: https://www.jmchemsci.com/article_172359.html