Aromatase mutation in men as a rare cause of osteoporosis: a case report and review of the literature

N.A. Stumper[1,2], H. Wientgen[1], L. Al-Hashimi[1,2], H.-W. Müller[3], S. Ohrndorf[2], T. Gaber[2], H. Siggelkow[4], P. Hoff[1,2,]

[1]Endokrinologikum Berlin am Gendarmenmarkt Berlin, Berlin, Germany; [2]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Rheumatology and Clinical Immunology, Berlin, Germany; [3]Amedes Genetik Göttingen, Göttingen, Germany; [4]Endokrinologikum Göttingen and Georg-August-Universität Göttingen, Göttingen, Germany.

Abstract

Objective

Oestrogen deficiency is a rare disease and leads inter alia to arthralgia and osteoporosis in men. The clinical relevance of aromatase to a functioning male metabolism has become evident since 1991, when cases of patients with oestrogen deficiency caused by aromatase mutation were first described. Only few cases are known so far, which will now be presented in a case report and review of the literature.

Methods

All available publications since the first description in 1991 dealing with loss-of-function aromatase mutation in men were summarised and our case report was added.

Results

The mutations that cause the aromatase protein to lose function leads to a rather heterogeneous clinical picture. It is, however, clear that oestrogens play a central role in male patients, especially in bone metabolism. Most frequently, tall stature, unclosed epiphyseal joints, and osteoporosis are detected in affected individuals as a consequence of the change in hormonal status.

Conclusion

As low oestrogen is associated with arthralgia, patients with aromatase mutation may be referred to a rheumatologist. Despite aromatase deficiency being a rare disease, the study of the effects of oestrogen on male bone development provides important insights for endocrine bone regulation. It has been demonstrated that androgens alone are not sufficient for adequate skeletal development in males. The described effects of loss of oestrogens are known from the aromatase inhibitor therapy in breast cancer treatment. This work highlights the important role of oestrogens in individual health and disease in men. Molecular effects of oestrogens on bone metabolism are summarised.

Key words

aromatase mutation, loss-of-function mutation, arthralgia, oestrogen, osteoporosis in men, unclosed epiphyseal plates, aromatase inhibitors

Nele A. Stumper
Hilke Wientgen, MD
Leith Al-Hashimi
Hans-Werner Müller, MD
Sarah Ohrndorf, MD
Timo Gaber, PhD
Heide Siggelkow, MD, Prof.
Paula Hoff, MD

Please address correspondence to:
Paula Hoff
Charité - Universitätsmedizin Berlin,
Charitéplatz 1,
10117 Berlin, Germany.
E-mail: paula.hoff@charite.de

Received on May 12, 2022; accepted in revised form on October 6, 2022.

Competing interests: none declared.

Introduction

The role of oestrogens in men has gained more attention over the last decades, and their importance for the health of the individual has been increasingly highlighted. Low oestrogen levels are associated with arthralgia (1-3). Postmenopausal women and women under the therapy with aromatase inhibitors can develop arthralgia and thus be referred to a rheumatologist to clarify an inflammatory rheumatic disease. But in rare cases men can also be affected by arthralgia caused by low oestrogen and present to a rheumatologist.

In the course of androgen biosynthesis, androgens are formed in four reaction steps and then converted to oestrogens. The key enzyme of this synthesis is aromatase (CYP19A1; OMIM 107910; GeneID 1588), a CYP450-dependent enzyme (Fig. 1) (4). Aromatase belongs to the group of (steroid) hydroxylases and is characterised by its comparably high affinity to androgens as a substrate, compared to other steroid hydroxylases (4). It catalyses the irreversible conversion (demethylation) of androgens to oestrogens. Aromatase is expressed in multiple tissues, including the ovaries, testes, placenta, adipose tissue, and osteoblasts. The testes synthesise only 15% of the circulating oestrogen; the remaining 85% result from peripheral aromatisation of androgen precursors in various tissues, such as bone tissue (4-6). Mutations in the CYP19A1 gene lead to a loss of enzyme activity and thus to a decrease in oestrogen levels, and are inherited in an autosomal recessive manner. The majority of documented cases result from single-base substitution in the exons (7). Aromatase deficiency is a rare disorder with an incidence of <1/100.000 (Orphanet, as specified in Feb. 2021 (8)). The molecular effects of a loss of aromatase activity are comparable to the effects of aromatase inhibitors widely used in hormone-sensitive breast cancer treatment (Fig. 1-2) (9, 10).

This study presents a novel case of a male patient with aromatase deficiency and a review of the literature.

Materials and methods

The patient described was admitted to our outpatient clinic. Data were obtained from a retrospective review of records. Laboratory values were measured in an accredited laboratory. Bone mineral density (BMD) was determined using dual energy x-ray absorptiometry (GE LUNAR DPX PRODIGY) at the lumbar region (L1-L4) and the left hip. Male reference values were employed for our male patient

Search strategy for review of the literature

The online database of medical articles MEDLINE (https://pubmed.ncbi.nlm.nih.gov) was taken as the primary source for the data search. In addition, suitable case reports and studies were searched via PRIMO, the library portal of the Charité-Universitätsmedizin Berlin.

The PubMed database was searched for "aromatase mutation AND man". All the publications we found that appeared from 1991 onwards were reviewed for suitability for use in our review. Language restrictions were not considered.

For the advanced search of PubMed, search terms were combined with Boolean operators to improve the precision of the results. The search terms we employed were: aromatase deficiency AND man, aromatase loss of function mutation AND man, aromatase mutation man, aromatase mutation men, aromatase deficiency NOT woman, aromatase loss of function mutation NOT woman.

Subsequently, the bibliographies of the studies were searched for articles that may not have been included in the results of the PubMed search. Finally, international databases were searched for ongoing or unpublished studies that might be of interest to the work. We thus discovered 12 publications that met our criteria.

Inclusion and exclusion criteria

All retrospective studies on aromatase mutation were included initially. Articles not written in German, English, or French were deemed ineligible.

Since aromatase mutation is a disease that has been investigated in about 30 publications to date, no common inclusion and exclusion criteria, such as those applied to assess the quality of clinical studies, could be developed. Therefore, all articles dealing with the effects of aromatase mutation in men

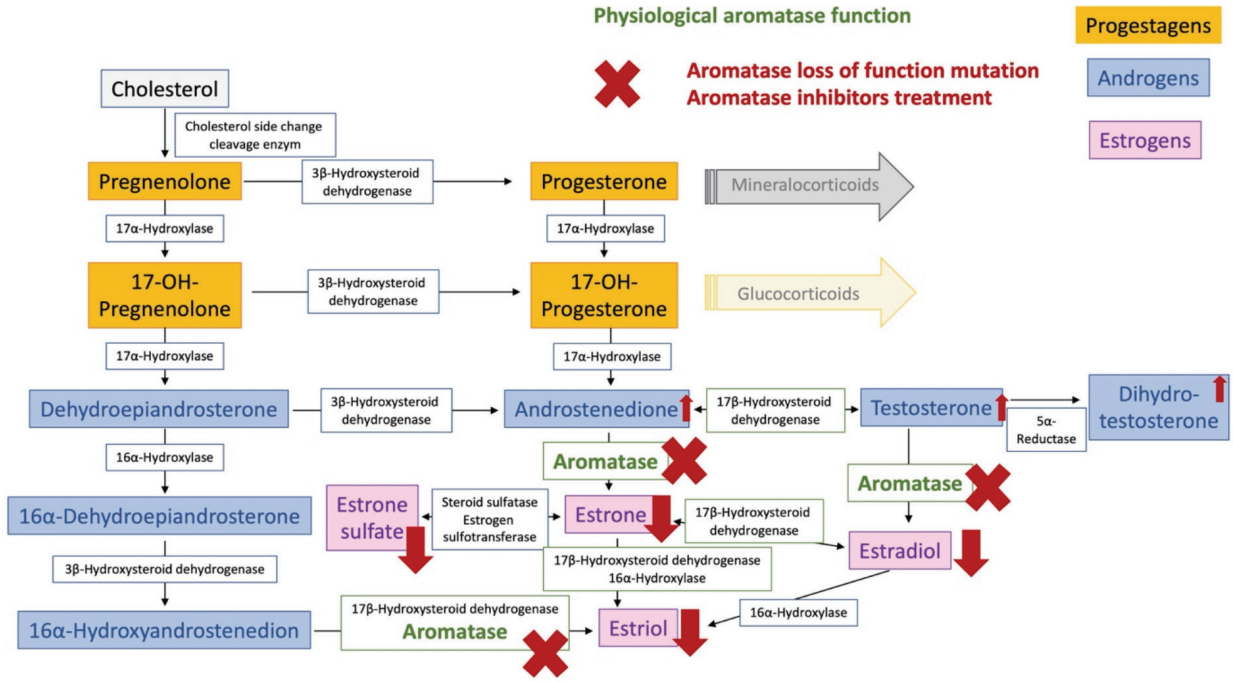

Fig. 1. Effects of aromatase and its inhibition on the steroid synthesis. Physiological aromatase function in the context of steroid synthesis, aromatase is indicated in green. Red crosses indicate the loss of function mutation of the aromatase or the treatment with aromatase inhibitors. Red arrows indicate the effects of the loss of function mutation of the aromatase or the treatment with aromatase inhibitors, oestrogens concentrations decrease (thick red arrow), androgens concentrations slightly increase (thin red arrows). Progestagens are indicated in yellow, androgens are indicated in blue and oestrogens are indicated in pink.

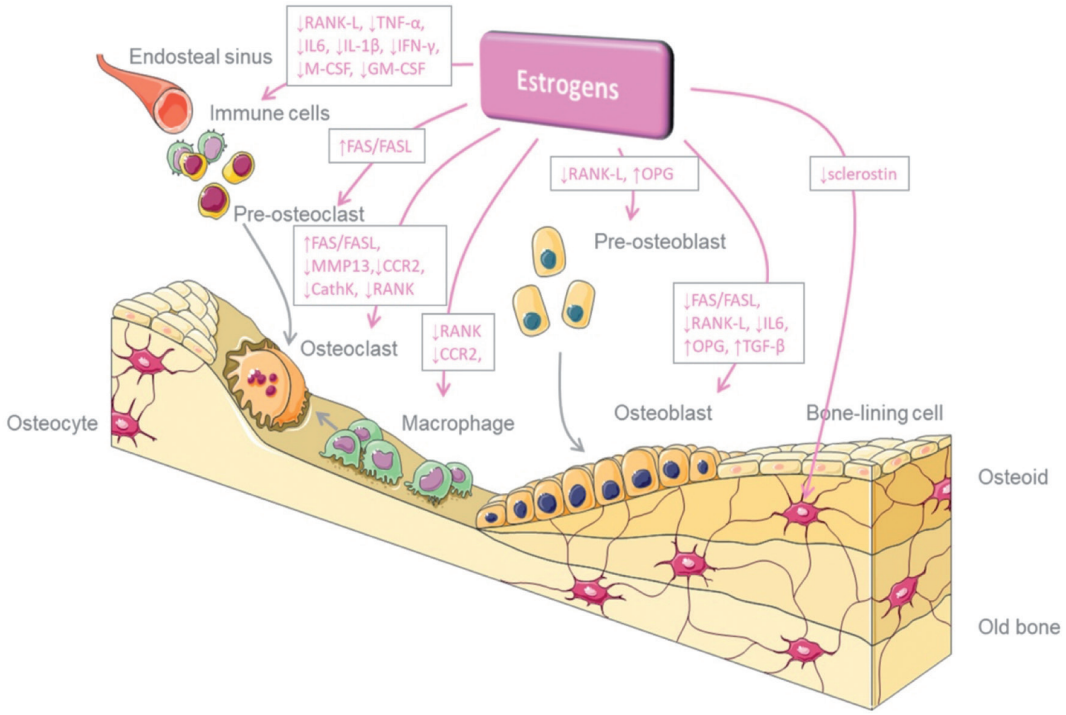

Fig. 2. Oestrogens affect bone homeostasis by promoting bone anabolic features while reducing bone catabolic effects. For the latter, Oestrogens enhance FAS/FASL interaction, stimulate osteoblasts (OBs) to produce TGF-β and thus, promote apoptosis of osteoclasts (OCs) and their progenitors (pOCs). They reduce RANK-L-induced differentiation by reducing RANK-L and M-CSF expression of immune cells, RANK and CCR2 expression of macrophages, and RANK-L expression of OBs as well as by induction of OPG production in OBs and mesenchymal stromal cells (MSCs). Furthermore, Oestrogens reduce the pro-inflammatory cytokine (*e.g.* TNF-α, IL-6, IL-1β, IFN-γ, GM-CSF)-mediated differentiation of monocytes and pOCs to Ocs as well as OC activity by reducing Cathepsin K (CathK) and MMP13 expression. Oestrogens promote bone anabolism by reducing FAS/FASL interaction and thus apoptosis of OBs and by promoting pOB and OB differentiation reducing RANKL and enhancing OPG and TGF-β. Finally, Oestrogens reduce apoptosis and the osteo anti-anabolic sclerostin secretion of osteocytes. FAS: fas receptor; FASL: fas ligand; GM-CSF: granulocyte-macrophage colony-stimulating factor; IFN-γ: interferon gamma; IL-1β: interleukin-1 beta; IL-6: interleukin-6; M-CSF: macrophage colony-stimulating factor; MMP13: matrix metalloproteinase 13; OPG: osteoprotegerin; RANK: receptor activator of nuclear factor ϰB; RANK-L: receptor activator of nuclear factor κB ligand; TGF-β: transforming growth factor beta; TNF-α: tumour necrosis factor alpha (36-40).

Table I. Effects of aromatase deficiency in men. Modified from Cooke *et al*. 2017, Lin 2007 (13, 24).

Author and type of publication	Age of patient	Mutation	Hormone profile	Effects on the mother	Influence on the skeletal system	Clinical effects	Therapy
Baykan *et al*. 2013 (25) Case report	27	• Point mutation	• LH und FSH ↑ • T normal • E2 not measurable • Total cholesterol and triglycerides elevated • Low HDL • BMI 25.7	No virilisation	Tall stature Open epiphyseal joints Rejuvenated bone age (15) Osteopenia/ Osteoporosis Recurrent bone fractures Bone pain	• Hepatosteatosis • Normal testicular volume and sperm count • Slightly reduced sperm motility • Ambiguous genitalia	• 25 µg transdermal oestradiol once in every three days
Bouchoucha *et al*. 2014 (4)	1-6 years old	• Point mutation ⇨ reduced activity of aromatase enzyme	• Normal hormone levels • FSH, LH, T, AMH und Inhibin B normal	No data	No data	• Hypospadias and bilateral cryptoorchidia • Normal male external genitalia with descended testes	No data
Bouillon *et al*. 2004 (26) Case report	17	• Frameshift mutation. ⇨ shortened protein	• Serum T + free T ↑ • LH and FSH upper normal range • E2 not measurable • Serum oestron low • BMI 27.7	No virilisation	Tall stature Open epiphyseal joints Rejuvenated bone age (12) Low BMD	• Normal testicular volume • Congenital hearing deficit (85% hearing loss)	• oestradiol valeriate at a daily oral dose of 1 mg
Carani *et al*. 1997 (15) Case report	31	• Point mutation • 0.4% residual activity	• T normal • FSH slightly ↑ • LH upper normal range • E2 not measurable • Dyslipidaemia • Insulin and glucose normal • BMI 27.6	No virilisation	Tall stature Genu valgum on both sides Bone pain Rejuvenated bone age (14.8) Open metacarpal and phalangeal epiphyseal joints	• Microorchidism • Infertility • Oligospermia with immobile spermatozoa • Hypospermatogenesis and sperm-cell arrest	• 50 µg / 25 µg of transdermal oestradiol twice weekly
Chen *et al*. 2015 (21) Case report	24	• Compound heterozygous point mutation ⇨ reduced aromatase activity	• LH, FSH and T normal • E2 not measurable	No virilisation	Tall stature Genu valgum Open epiphyseal joints Osteopenia Low BMD Rejuvenated bone age (16-18)	• Testicular size, sperm count, and viability normal	• 25 µg transdermal oestradiol twice per week for 6 months • Then 0.3 mg daily
Deladoëy *et al*. 1997 (18) Case report	Child	• Base pair deletion in CYP 19 gene • Truncated, inactive protein	• Free serum T normal • Serum LH, FSH normal • E2 not measurable • Androstenedione high at birth, falls after a month	Virilisation	No data	• Normal testicular descent	• No data
Hermann *et al*. 2002 (16) Case report	27	• Frameshift mutation ⇨ stop code • Truncated protein	• T, androstenedione and FSH ↑ • LH normal • E2 and estrol low • Plasma glucose and insulin normal • Dyslipidemia • BMI 30.9	Virilisation	Tall stature Genu valgum High linear growth Low BMD Kyphoscoliosis Pectus carniatus	• Oligospermia with reduced sperm motility • Normal testicular volume • Normal morphology and vitality of spermatozoa	• 50 µg transdermal oestradiol twice weekly for 3 months • Then 25 µg twice weekly
Lanfranco *et al*. 2008 (27) Case report	26	• Compound heterozygous point mutation ⇨ truncated inactive protein	• FSH ↑ • LH and T normal • E2 not measurable • High fasting insulin • Insulin resistance • Dyslipidaemia • BMI 29.3	No virilisation	Tall stature Open epiphyseal joints Genu valgum Osteopenia Low BMD Rejuvenated bone age (15.5)	• Normal testicular volume and sperm count • Slightly reduced sperm motility • Cryptoorchidism on the right testis • Fat liver • Acanthosis nigricans	• transdermal oestradiol
Maffei *et al*. 2004 (28) Case report	29	• Point mutation • Truncated protein	• T and LH normal • FSH ↑ • E2 not measurable • Insulin upper normal range • Glucose normal • BMI 25.4	No virilisation	Tall stature Continuing linear growth Diffuse bone pain Genu valgum Open metacarpal and phalangeal epiphyseal joints Rejuvenated bone age (15) Osteoporosis Low BMD Acanthosis nigricans	• Bilateral cryptorchidism • Microorchid testis in the inguinal canal • Abnormal semniferous tubules • Atrophied and degenerated epithelium	• transdermal oestradiol, 25 µg twice weekly for 6 months • transdermal oestradiol, 50 µg twice weekly for 6 months
Maffei *et al*. 2007 (29) Case report	25	• 2-point mutations	• T and LH normal • FSH ↑ • E2 not measurable • Hyperinsulinaemia • Obesity • Insulin resistance • Dyslipidaemia • BMI 29.3	No virilisation	Tall stature Continuing linear growth Diffuse bone pain Genu valgum Open epiphyseal joints Rejuvenated bone age (15.3) Osteopenia/ osteoporosis Low BMD	• Normal testicular volume • Hypospermia • Acanthosis nigricans • Hepatomegaly • Non-alcoholic fatty liver (NAFL)	• No data

Author and type of publication	Age of patient	Mutation	Hormone profile	Effects on the mother	Influence on the skeletal system	Clinical effects	Therapy
Miedlich *et al*. 2016 (7) Review	25	• Point mutation ⇨ truncated, inactive protein	• FSH and LH normal • T upper normal range • E2 not measurable • Insulin, glucose and lipid profile normal	Virilisation	Tall stature Bone abnormalities	• Testicular size and libido normal • Moderate acanthosis nigricans	• therapy with oestradiol
Morishima *et al*. 1995 (30) Case report	24	• Point mutation • 0,2% residual activity	• Hyperinsulinism • LDL ↑, HDL ↓ • T, LH and FSH ↑ • E2 and E1 ↓ • Abnormal glucose and lipid metabolism • Dyslipidaemia • BMI 32.5	Virilisation Hirsutism and acne	Tall stature Osteopenia/ osteoporosis Open epiphyseal joints Rejuvenated bone age (14) Low BMD	• Macroorchidia • Tanner stage 5 pubic hair	• No data
Stumper *et al*. 2022 Case report and Review	32	• Point mutation in intron 9 in homozygous form (CYP19 A1(NM_000103.3): c.1263+1G>T).	• LDL normal, HDL ↓ • T, Prolactin, LH and FSH ↑ • Triglycerides ↑ • E2 ↓ • Cholesterol ↑	Unknown	Tall stature Continuing linear growth shaft fracture of the metacarpal bone IV and a proximal phalanx fracture of the middle finger Open epiphyseal plates Genu valgum	• Normal sperm count T • esticular size normal	• transdermal oestradiol, 25-50 µg

were included until further notice. Furthermore, papers that did not primarily address the aromatase mutation, but also the consequences of therapy with aromatase inhibitors or oestrogen replacement therapy were also included. Animal studies and studies dealing exclusively with the effects of the mutation in women were excluded, as we focused on the loss-of-function aromatase mutation in men.

Data acquisition and quality assessment

The publications were read in detail several times and the data summarised in Table I. Peer-reviewed publications were selected. We followed up to ensure that the Charité statutes on ensuring good scientific practice were adhered to.

Case report

We report a 32-year-old male patient who first presented at the "Endokrinologikum Berlin" medical care center in November 2017. The patient was referred to us to clarify arthralgia and suspected acromegaly on the grounds of his excessively tall growth. The patient measured 172 cm at age 23 and grew to his current height of 186 cm by age 27. His height has remained constant since then. During the same time, his shoe size increased from 42 (UK 8/ US 9) to the current 45 (UK 10 ½ / US 11 ½). His parents and his half-brother were about a head smaller in height.

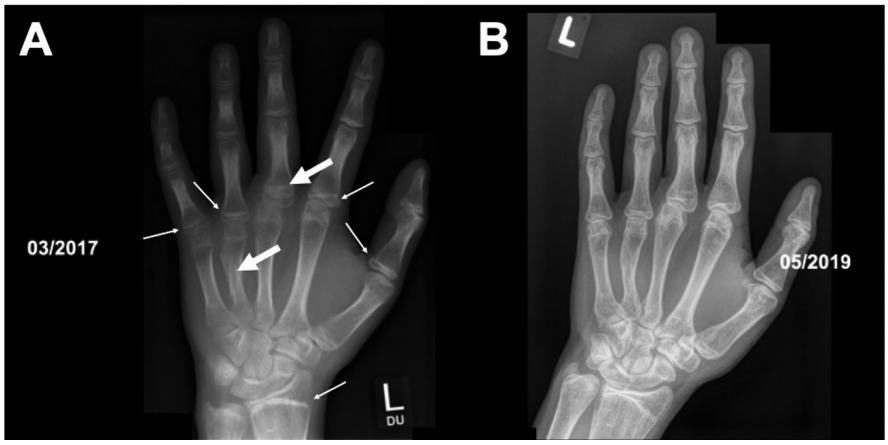

Fig. 3. X-ray of a patient with aromatase deficiency: (**A**) left hand before and (**B**) after therapy with oestrogen; thick arrows label fractures, thin arrows label some unclosed epiphyseal plates.

Furthermore, the patient reported a shaft fracture of metacarpal bone IV and a proximal phalanx fracture of the middle finger (Fig. 3A, thick arrows) detected by x-ray in March 2017. In this x-ray, surprisingly, the lack of epiphyseal closure was also noticeable (Fig. 3A, thin arrows indicating examples).

Physical examination revealed the following: his heart, lung, and abdomen were without pathological findings.

Clinically, there were no signs of swollen joints and no signs of acromegaly, such as widened and thickened nose, prominent cheekbones, thick lips, or mandibular overgrowth (11).

In contrast to what one would expect in acromegaly as a result of increased secretion of growth hormone, the concentration of insulin-like growth factor 1 (IGF1) was not found to be increased (IGF1 143 µg/l, standard range 120–400 µg/l). However, laboratory results revealed an elevated testosterone level (testosterone 8.42 ng/ml, standard range 2.49–8.36 ng/ml). The oestrogen value was determined as lying below the detection limit.

This constellation of results led us to suspect an aromatase deficiency, and the patient underwent genetic testing: A mutation in intron 9 was detected in homozygous form in the region of the CYP19A1 gene examined (CYP19A1(NM_000103.3):c.1263+1G>). The mutation is listed as a disease-causing mutation in the Human Gene Mutation Database (HGMD). Genetic testing confirmed our suspicion, and we diagnosed a congenital aromatase deficiency in our patient.

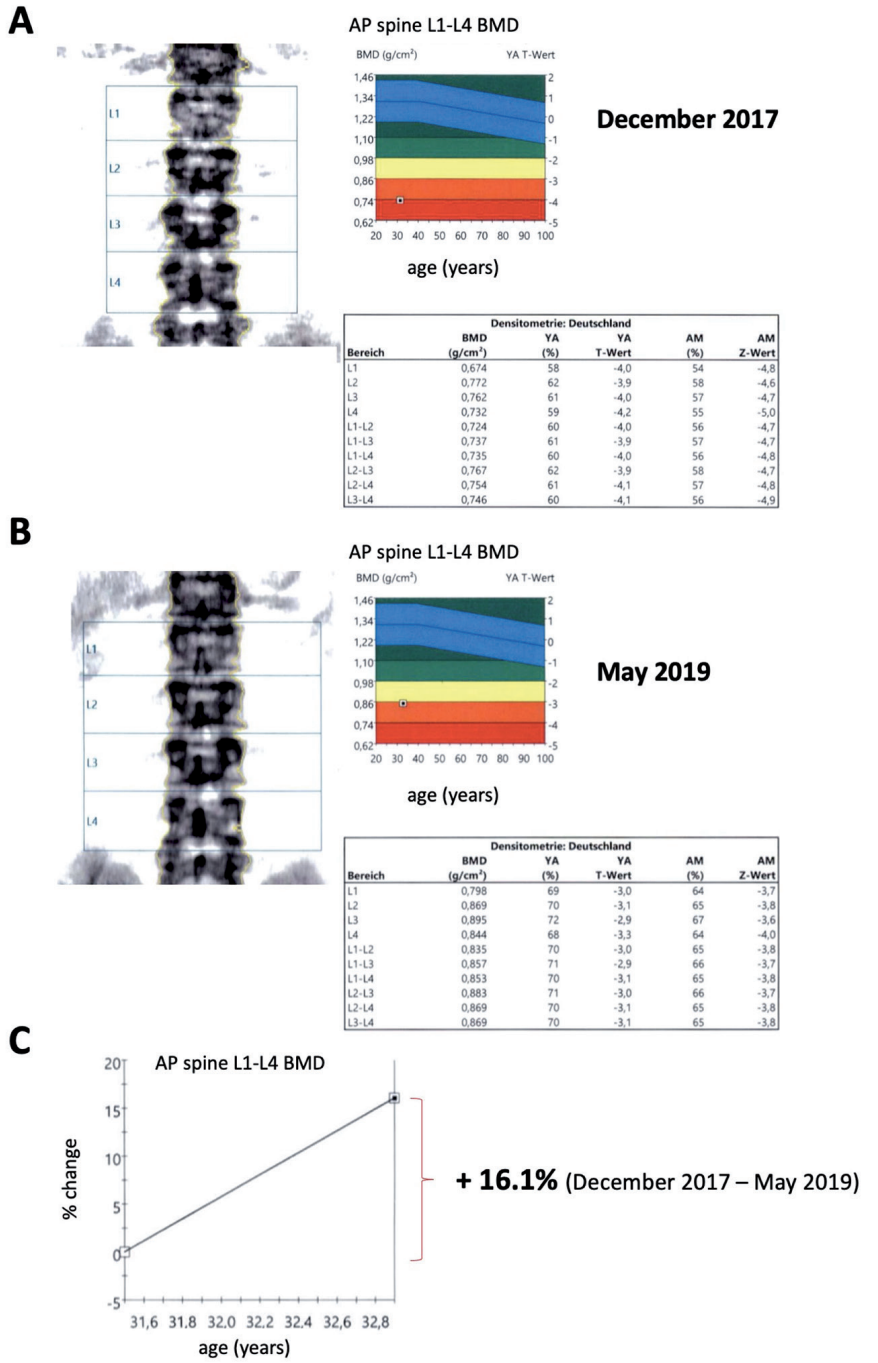

Fig. 4. BMD of the spine of a patient with aromatase deficiency (**A**) before (December 2017) and (**B**) after therapy with oestradiol for 17 months (May 2019). (**C**) The increase in bone density is visualised.

The fractures diagnosed in the left hand in March 2017 were not associated with a high-impact trauma. Furthermore, an aromatase deficiency is commonly associated with osteoporosis. This is why the patient underwent a bone mineral density (BMD) measurement using dual energy x-ray absorptiometry in December 2017. Examination of the lumbar region (L1-L4) revealed a Z-score of -4.8 with lowest Z-score of -5.0 at L4. Examination of the left femur resulted in a Z-score of -2.4, with the femoral neck returning a Z-Score of -2.5 (male reference values) (Fig. 4a).

Therapy with oestradiol in transdermal application (25–50 ug/d) was initiated in December 2017. The defined therapeutic target was set for estradiol as greater than 40 pg/ml. In spite of multiple adjustments to the dose of oestradiol, values in our target range were not achieved until 2019. Often, they remained below the detection limit (Fig. 5). This is best explained by fluctuations in patient compliance. In Figure 5 we have shown the laboratory values of oestradiol, testosterone, luteinising hormone (LH), follicle-stimulating hormone (FSH), and the liver enzymes Aspartate-aminotransferase (AST) and alanine-aminotransferase (ALT) over the time. After treatment with oestradiol, testosterone, LH and FSH decreased to normal levels except for April and December 2021, when oestradiol was again found under detection limit (most likely due to non-compliance). Due to the frequent finding of metabolic syndrome in patients with aromatase mutation we also show the liver enzymes. While AST was within the normal range over time, ALT as the more liver specific enzyme usually exceeded the upper limit (however, bad lifestyle also plays a role). The HbA1c was always within the normal range.

However, BMD in our patient did increase by 16.1%, in response to the therapy from December 2017 to May 2019 (Fig. 4b-c).

Review of the literature

Cases of men with aromatase mutation reported previously have revealed that some symptoms occur in almost all patients, despite the rather heterogeneous clinical picture (Table I).

Clinical symptoms

In summary, the clinical effects of aromatase mutation on men are generally considered milder than on women. The external genitalia are not affected by clinical changes in males, despite elevated androgen concentrations. Postnatally, the high androgen level and oestrogen deficit result in a variable clinical picture (12). In contrast to females, the disease is not diagnosed at birth in males. The average age on diagnosis in men is approximately 21 years (13, 14). They usually present to the physician with excessive growth, metabolic disturbances, and unclosed epiphyseal plates (4, 15-17). To date, only one male patient has had the defect recognised at birth, through expertise and caused by maternal virilisation (18).

The first signs of the mutation may be

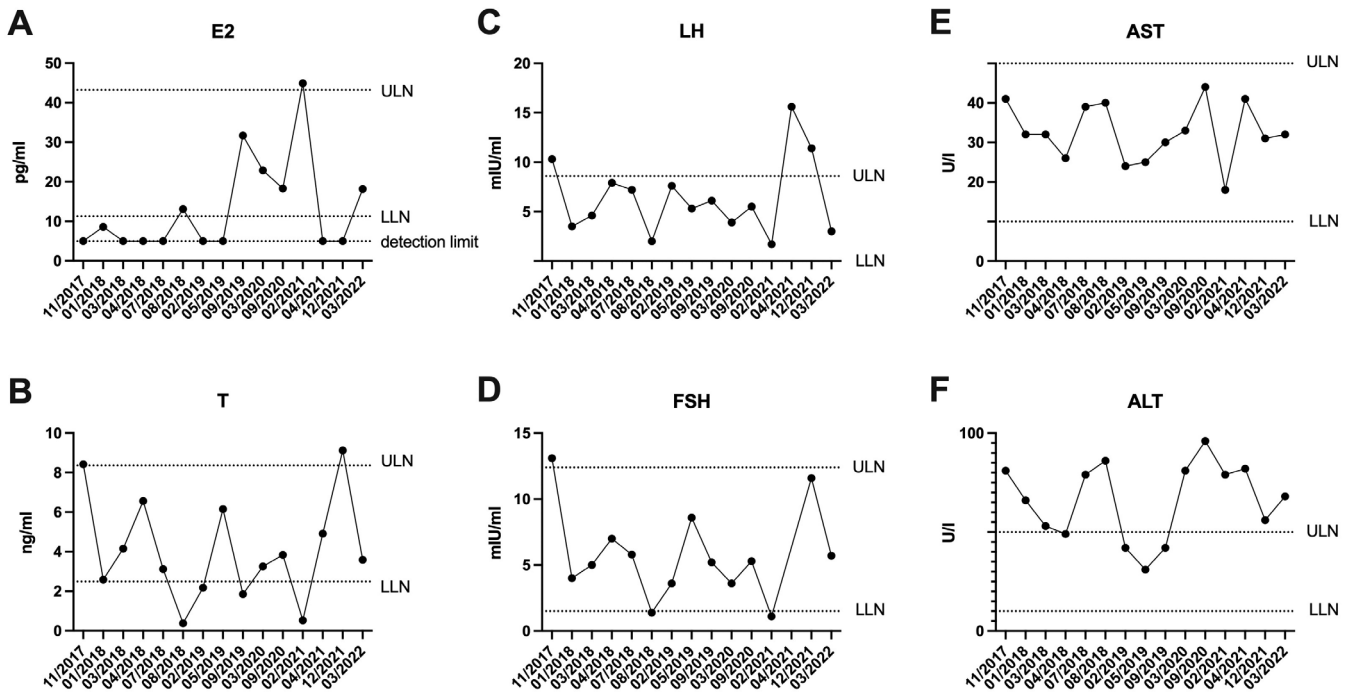

Fig. 5. Laboratory values over time. E2: oestradiol (**A**), T: testosterone (**B**), LH: luteinising hormone (**C**), FSH: follicle-stimulating hormone (**D**), AST: aspartate-aminotransferase (**E**) and ALT: Alanine-aminotransferase (**F**). ULN: upper limit of normal, LLN: lower limit of normal.

detected in the mother already during pregnancy. These suffer from virilisation because androgens are no longer aromatised in the placenta. This causes high concentrations of androstenedione and testosterone to enter both the maternal and fetal circulations (18). In affected individuals, symptoms appear between the twelfth and thirtieth week of pregnancy and manifest as clitoral hypertrophy, severe acne, hirsutism, and a deep voice (19). Normally, these symptoms regress in the mother during the first weeks postpartum. However, it has been demonstrated that even a residual 1% of the original aromatase activity is sufficient to prevent virilisation of the mother (20). During the second half of pregnancy, extremely low (0.8–1.1% of normal) E2 and oestriol levels lead to the confirmation of the diagnosis (19).

Childhood is usually free of symptoms for the male. The external genitalia develop normally, and the course of puberty is unremarkable. However, young males become conspicuous by their tall stature, excessive growth, and eunuchoid body proportions with long arms and an increased proportion of visceral fat (21). Radiographs often reveal the incomplete or absent closure of the epiphyseal plates, especially in the metacarpal and phalangeal regions (15). Clinically, the condition genu valgum is also typical (21). Hypospadias, undescended testes, and micro- as well as macro-orchidia are also observed (19). Various degrees of severity of testicular dysfunction have also been described; it is assumed that oestrogen deficiency alters testicular development and function in adults (12).

Furthermore, oestrogen deficiency results in altered bone homeostasis. Osteopenia and even severe osteoporosis are often observed, as well as a sometimes severely reduced bone mineral density (22). Figure 4a depicts the bone mineral density of our patient prior to initiating therapy (32-year-old patient with "loss-of-function" aromatase mutation); Figure 4b after 1.5 years of successful therapy. An increase in bone mineral density of 16% is clearly visible within only 1.5 years (Fig. 4c).

Oestrogen deficiency causes the epiphyseal plates not to close, even after puberty is complete. In summary, androgens alone are not sufficient to induce normal skeletal development (23).

Laboratory values

At the metabolic level, we observe an abnormal lipid profile and insulin resistance. One also finds altered levels of luteinising hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), and oestradiol (E2) (4, 7, 15, 16, 18, 21, 26-30), as portrayed in Figure 6.

The gonadotropins LH and FSH are produced centrally in the adrenal pituitary gland. They are part of the hypothalamic-pituitary-gonadal (HPG) axis, which induces in males the synthesis of androgens in Leydig cells and the aromatisation of these to oestrogens in Sertoli cells, among other things (5). In the case of aromatase mutation, the altered androgen level may affect the feedback mechanisms of the HPG axis and lead to altered levels of T, LH, and FSH.

Figure 7 portrays the E2 levels in all 13 male patients at the time of diagnosis. In seven patients, the levels were below the detection limit (18, 21, 26-29). There was no information at all on E2 for one patient (2). In four patients, E2 levels were below the lower limit of the reference range (7, 15, 16, 30).

Therapy of oestrogen deficiency

The therapy of choice is E2 administered transdermally. With therapy, most symptoms disappear, the epiphyseal joints close, and the rate of bone remodeling decreases. Figure 3 depicts the complete closure of the epiphyseal

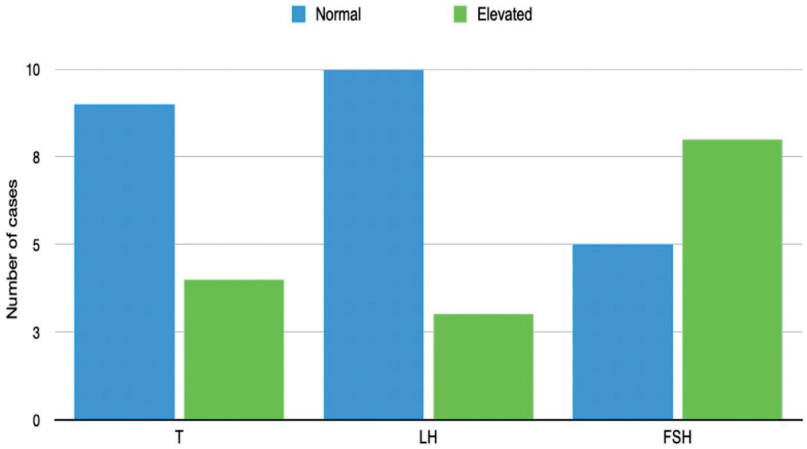

Fig. 6. Number of patients with normal (blue) or elevated (green) testosterone (T), luteinising hormone (LH), and follicle-stimulating hormone (FSH) at the time of diagnosis of aromatase mutation, n=13 (12 cases reported previously and our reported patient).

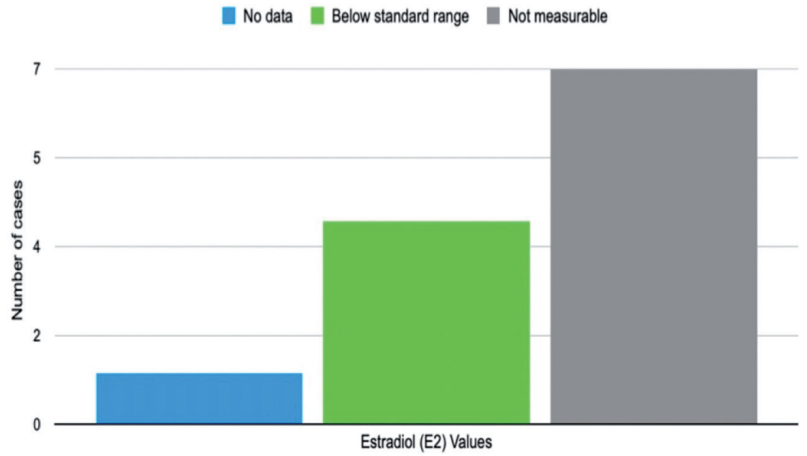

Fig. 7. Number of patients with E2 below standard range (green), E2 below detection limit (grey), or no measurement of E2 at time of diagnosis (blue) of aromatase mutation, n=13 (12 cases reported previously and our reported patient).

joints in a 32-year-old patient with aromatase mutation after 27 months of treatment with oestrogen.

Discussion

Oestrogens exhibit an important role not only in females but also in male individuals. Especially the bone metabolism is affected by the mutations that cause the aromatase protein to lose function. As low oestrogen levels are associated with musculoskeletal pain (1-3), these patients can also be presented to a rheumatologist. To clarify the joint pain, the rheumatologist would arrange for a laboratory and x-ray of hands and feet. Laboratory tests would not show any abnormalities such as systemic inflammation or autoantibodies. But x-ray would show rarified bone structure and open epiphyseal joints. The combination of arthralgia and open epiphyseal joints points toward an aromatase mutation. When low oestrogen levels would confirm the suspected diagnosis, next genetic testing could prove the mutation. The clinical effects in male patients carrying this mutation are comparable with patients suffering from breast cancer, mainly women, being treated with aromatase inhibitors (9, 10). The effect on the oestrogen synthesis of men with aromatase mutation and patients under treatment with aromatase inhibitors are summarised in Figure 1 and 2. In the process of steroid synthesis, the loss of function of the aromatase or the aromatase inhibition treatment leads to blocked oestrogen synthesis (Fig. 1) (9, 10). Patients treated with aromatase inhibitors are usually adults (mostly women), in which the epiphyseal joints are already closed, thus treatment with aromatase inhibitors does not lead to growth in length. This is in contrast to men with aromatase loss of function mutation where the growth in length is a typical sign as these patients carry the mutation from birth and the epiphyseal joints do not close without oestrogen. For the same reason aromatase inhibitors can be used in male children with short stature. The treatment leads to improved height outcomes (31-33).

In both patient groups, males with mutated aromatase and hormone sensitive breast cancer patients under aromatase inhibitor treatment, the positive effects of oestrogens on bone are restricted (Fig. 2) (34-40). Patients suffering from aromatase loss-of-function mutations develop severe osteoporosis. Further hall marks are tall stature and unclosed epiphyseal joints. Treatment with oestradiol dissolves the consequences of the disease. In patients undergoing an aromatase inhibitor treatment due to hormone sensitive breast cancer the blockade of oestrogen production is of course desired. But as these patients are also at risk of reduced bone density and increased fracture risk, we must consider osteoporosis prophylaxis (9). Bone density and bone metabolism are evaluated and whenever needed a treatment with, for example, bisphosphonates, will be started. Having understood the underlying mechanisms of a blocked or, as in our case, not functioning, aromatase has a great impact on the medical decisions in prophylaxis of osteoporosis and fractures.

Key messages

- Low oestrogen levels can be associated with musculoskeletal pain.
- Aromatase mutation in men leads to severe osteoporosis, tall stature and unclosed epiphyseal joints.
- The effects of the aromatase mutation on bone metabolism are comparable to the treatment of hormone sensitive breast cancer patients with aromatase inhibitors.
- Aromatases mutation is a rare disease and is treated with estradiol. The mechanism of action emphasises the need for osteoporosis prophylaxis in breast cancer patients treated with aromatase inhibitors.

References

1. LINTERMANS A, NEVEN P: Pharmacology of arthralgia with deprivation. *Steroids* 2011; 76(8): 781-5. https://doi.org/10.1016/j.steroids.2011.02.034
2. REINBOLT RE, SONIS S, TIMMERS CD *et al*.: Genomic risk prediction of aromatase inhibitor-related arthralgia in patients with breast cancer using a novel machine-learning algorithm. *Cancer Med* 2018; 7(1): 240-53. https://doi.org/10.1002/cam4.1256
3. WATT FE: Musculoskeletal pain and menopause. *Post Reprod Health* 2018; 24(1): 34-43. https://doi.org/10.1177/2053369118757537
4. BOUCHOUCHA N, SAMARA-BOUSTANI D, PANDEY AV *et al*.: Characterization of a novel CYP19A1 (aromatase) R192H mutation causing virilization of a 46,XX newborn, undervirilization of the 46,XY brother, but no virilization of the mother during pregnancies. *Mol Cell Endocrinol* 2014; 390(1-2): 8-17. https://doi.org/10.1016/j.mce.2014.03.008
5. BLAKEMORE J, NAFTOLIN F: Aromatase: contributions to physiology and disease in women and men. *Physiology* (Bethesda) 2016; 31(4): 258-69. https://doi.org/10.1152/physiol.00054.2015.
6. GENNARI L, NUTI R, BILEZIKIAN JP: Aromatase activity and bone homeostasis in men. *J Clin Endocrinol Metab* 2004; 89(12): 5898-907. https://doi.org/10.1210/jc.2004-1717
7. MIEDLICH SU, KARAMOOZ N, HAMMES SR: Aromatase deficiency in a male patient - Case report and review of the literature. *Bone* 2016; 93: 181-6. https://doi.org/10.1016/j.bone.2016.09.024
8. INSERM_US14. Orhanet [Orphanet Website]. 2022 [updated 2022-01-21; cited 2022-1-22]. Available from: https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=DE&data_id=8670
9. RACHNER TD, COLEMAN R, HADJI P, HOFBAUER LC: Bone health during endocrine therapy for cancer. *Lancet Diabetes Endocrinol* 2018; 6(11): 901-10. https://doi.org/10.1016/S2213-8587(18)30047-0
10. RAMCHAND SK, CHEUNG YM, YEO B, GROSSMANN M: The effects of adjuvant endocrine therapy on bone health in women with breast cancer. *J Endocrinol* 2019; 241(3): R111-R24. https://doi.org/10.1530/JOE-19-0077
11. CHANSON P, SALENAVE S: Acromegaly. *Orphanet J Rare Dis* 2008; 3: 17. https://doi.org/10.1186/1750-1172-3-17
12. BELGOROSKY A, GUERCIO G, PEPE C, SARACO N, RIVAROLA MA: Genetic and clinical spectrum of aromatase deficiency in infancy, childhood and adolescence. *Horm Res* 2009; 72(6): 321-30. https://doi.org/10.1159/000249159
13. COOKE PS, NANJAPPA MK, KO C, PRINS GS, HESS RA: Estrogens in male physiology. *Physiol Rev* 2017; 97(3): 995-1043. https://doi.org/10.1152/physrev.00018.2016
14. OZEN S, ATIK T, KORKMAZ O *et al*.: Aromatase deficiency in two siblings with 46,XX karyotype raised as different genders: a novel mutation (p.R115X) in the CYP19A1 gene. *J Clin Res Pediatr Endocrinol* 2020; 12(1): 109-12. https://doi.org/10.4274/jcrpe.galenos.2019.2018.0198
15. CARANI C, QIN K, SIMONI M *et al*.: Effect of testosterone and estradiol in a man with aromatase deficiency. *N Engl J Med* 1997; 337(2): 91-5. https://doi.org/10.1056/NEJM199707103370204
16. HERRMANN BL, SALLER B, JANSSEN OE *et al*.: Impact of estrogen replacement therapy in a male with congenital aromatase deficiency caused by a novel mutation in the CYP19 gene. *J Clin Endocrinol Metab* 2002; 87(12): 5476-84. https://doi.org/10.1210/jc.2002-020498
17. ROCHIRA V, FAUSTINI-FUSTINI M, BALESTRIERI A, CARANI C: Estrogen replacement therapy in a man with congenital aromatase deficiency: effects of different doses of transdermal estradiol on bone mineral density and hormonal parameters. *J Clin Endocrinol Metab* 2000; 85(5): 1841-5. https://doi.org/10.1210/jcem.85.5.6583
18. DELADOEY J, FLUCK C, BEX M, YOSHIMURA N, HARADA N, MULLIS PE: Aromatase deficiency caused by a novel P450arom gene mutation: impact of absent estrogen production on serum gonadotropin concentration in a boy. *J Clin Endocrinol Metab* 1999; 84(11): 4050-4. https://doi.org/10.1210/jcem.84.11.6135
19. BULUN SE: Aromatase and estrogen receptor alpha deficiency. *Fertil Steril* 2014; 101(2): 323-9. https://doi.org/10.1016/j.fertnstert.2013.12.022
20. GRUMBACH MM, AUCHUS RJ: Estrogen: consequences and implications of human mutations in synthesis and action. *J Clin Endocrinol Metab* 1999; 84(12): 4677-94. https://doi.org/10.1210/jcem.84.12.6290
21. CHEN Z, WANG O, NIE M *et al*.: Aromatase deficiency in a Chinese adult man caused by novel compound heterozygous CYP19A1 mutations: effects of estrogen replacement therapy on the bone, lipid, liver and glucose metabolism. *Mol Cell Endocrinol* 2015; 399: 32-42. https://doi.org/10.1016/j.mce.2014.09.016
22. UNAL E, YILDIRIM R, TAS FF, DEMIR V, ONAY H, HASPOLAT YK: Aromatase deficiency due to a novel mutation in CYP19A1 gene. *J Clin Res Pediatr Endocrinol* 2018; 10(4): 377-81. https://doi.org/10.4274/jcrpe.0011
23. SHOZU M, AKASOFU K, HARADA T, KUBOTA Y: A new cause of female pseudohermaphroditism: placental aromatase deficiency. *J Clin Endocrinol Metab* 1991; 72(3): 560-6. https://doi.org/10.1210/jcem-72-3-560
24. LIN L, ERCAN O, RAZA J *et al*.: Variable phenotypes associated with aromatase (CYP19) insufficiency in humans. *J Clin Endocrinol Metab* 2007; 92(3): 982-90. https://doi.org/10.1210/jc.2006-1181
25. BAYKAN EK, ERDOGAN M, OZEN S, DARCAN S, SAYGILI LF: Aromatase deficiency, a rare syndrome: case report. *J Clin Res Pediatr Endocrinol* 2013; 5(2): 129-32. https://doi.org/10.4274/Jcrpe.970
26. BOUILLON R, BEX M, VANDERSCHUEREN D, BOONEN S: Estrogens are essential for male pubertal periosteal bone expansion. *J Clin Endocrinol Metab* 2004; 89(12): 6025-9. https://doi.org/10.1210/jc.2004-0602
27. LANFRANCO F, ZIRILLI L, BALDI M *et al*.: A novel mutation in the human aromatase gene: insights on the relationship among serum estradiol, longitudinal growth and bone mineral density in an adult man under estrogen replacement treatment. *Bone* 2008; 43(3): 628-35. https://doi.org/10.1016/j.bone.2008.05.011
28. MAFFEI L, MURATA Y, ROCHIRA V *et al*.: Dysmetabolic syndrome in a man with a novel mutation of the aromatase gene: effects of testosterone, alendronate, and estradiol treatment. *J Clin Endocrinol Metab* 2004; 89(1): 61-70. https://doi.org/10.1210/jc.2003-030313
29. MAFFEI L, ROCHIRA V, ZIRILLI L *et al*.: A novel compound heterozygous mutation of the aromatase gene in an adult man: reinforced evidence on the relationship between congenital oestrogen deficiency, adiposity and the metabolic syndrome. *Clin Endocrinol* (Oxford) 2007; 67(2): 218-24. https://doi.org/10.1111/j.1365-2265.2007.02864.x
30. MORISHIMA A, GRUMBACH MM, SIMPSON ER, FISHER C, QIN K: Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. *J Clin Endocrinol Metab* 1995; 80(12): 3689-98. https://doi.org/10.1210/jcem.80.12.8530621
31. HERO M: Aromatase inhibitors in the treatment of short stature. *Endocr Dev* 2016; 30: 130-40. https://doi.org/10.1159/000439338
32. MAURAS N, ROSS JL, GAGLIARDI P *et al*.: Randomized trial of aromatase inhibitors, growth hormone, or combination in pubertal boys with idiopathic, short stature. *J Clin Endocrinol Metab* 2016; 101(12): 4984-93. https://doi.org/10.1210/jc.2016-2891
33. MCGRATH N, O'GRADY MJ: Aromatase inhibitors for short stature in male children and adolescents. *Cochrane Database Syst Rev* 2015; (10): CD010888. https://doi.org/10.1002/14651858.CD010888.pub2
34. KHOSLA S: Estrogen versus FSH effects on bone metabolism: evidence from interventional human studies. *Endocrinology* 2020; 161(8). https://doi.org/10.1210/endocr/bqaa111
35. KHOSLA S, MONROE DG: Regulation of bone metabolism by sex steroids. *Cold Spring Harb Perspect Med* 2018; 8(1). https://doi.org/10.1101/cshperspect.a031211
36. ANAGNOSTIS P, BOSDOU JK, VAITSI K, GOULIS DG, LAMBRINOUDAKI I: Estrogen and bones after menopause: a reappraisal of data and future perspectives. *Hormones (Athens)* 2021; 20(1): 13-21. https://doi.org/10.1007/s42000-020-00218-6
37. BINDER NB, NIEDERREITER B, HOFFMANN O *et al*.: Estrogen-dependent and C-C chemokine receptor-2-dependent pathways determine osteoclast behavior in osteoporosis. *Nat Med* 2009; 15(4): 417-24. https://doi.org/10.1038/nm.1945
38. HAYASHI M, NAKASHIMA T, YOSHIMURA N, OKAMOTO K, TANAKA S, TAKAYANAGI H: Autoregulation of osteocyte Sema3A orchestrates estrogen action and counteracts bone aging. *Cell Metab* 2019; 29(3): 627-37 e5. https://doi.org/10.1016/j.cmet.2018.12.021
39. NOVACK DV: Estrogen and bone: osteoclasts take center stage. *Cell Metab* 2007; 6(4): 254-6. https://doi.org/10.1016/j.cmet.2007.09.007
40. WEITZMANN MN, PACIFICI R: Estrogen deficiency and bone loss: an inflammatory tale. *J Clin Invest* 2006; 116(5): 1186-94. https://doi.org/10.1172/JCI28550