Aromatase Mutation in Men: A Case Report and Review of the Literature

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Keywords:
Aromatase mutation; loss-of-function mutation; estrogen; osteoporosis in men, unclosed epiphyseal plates; Aromatase inhibitors

1. Abstract

1.1. Background: The clinical relevance of aromatase to a functioning male metabolism has become evident since 1991, when cases of patients with estrogen 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.

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

1.3. Results: The mutations that cause the aromatase protein to lose function lead to a rather heterogeneous clinical picture. It is, however, clear that estrogens 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.

1.4. Conclusions: Despite aromatase deficiency being a rare disease, the study of the effects of estrogen 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 estrogens are known from the aromatase inhibitor therapy in breast cancer treatment. This work highlights the important role of estrogens in individual health and disease in men. Molecular effects of estrogens on bone metabolism are summarized.

2. Introduction

The role of estrogens in men has gained more attention over the last decades, and their importance for the health of the individual has been increasingly highlighted.

In the course of androgen biosynthesis, androgens are formed in four reaction steps and then converted to estrogens. The key enzyme of this synthesis is aromatase (CYP19A1; OMIM 107910; GeneID 1588), a CYP450-dependent enzyme (summarized in figure 5) [1]. Aromatase belongs to the group of (steroid) hydroxylases and is characterized by its comparably high affinity to androgens as a substrate, compared to other steroid hydroxylases [1]. It catalyzes the irreversible conversion (demethylation) of androgens to estrogens. Aromatase is expressed in multiple tissues, including the ovaries, testes, placenta, adipose tissue, and osteoblasts. The testes synthesize only 15% of the circulating estrogen; the remaining 85% result from peripheral aromatization of androgen precursors in various tissues, such as bone tissue [1-3].

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in the CYP19A1 gene lead to a loss of enzyme activity and thus to a decrease in estrogen levels, and are inherited in an autosomal recessive manner. The majority of documented cases results from single-base substitution in the exons [4]. Aromatase deficiency is a rare disorder with an incidence of <1/100,000 (Orphanet, as specified in February 2021 [5]. 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 (figure 5+6) [6, 7].

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

3. 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 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. Furthermore, the patient reported a shaft fracture of metacarpal bone IV and a proximal phalanx fracture of the middle finger (Figure 1A, thick arrows) detected by X-ray in March 2017. In this X-ray, surprisingly, the lack of epiphyseal closure was also noticeable (Figure 1A, thin arrows indicating examples).

Physical examination revealed the following: his heart, lung, and abdomen were without pathological findings. Clinically, there were no signs of acromegaly, such as widened and thickened nose, prominent cheekbones, thick lips, or mandibular overgrowth [8]. 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 estrogen 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>T). 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.

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 T-score of -4.0 with lowest T-score of -5.0 at L4. Examination of the left femur resulted in a T-score of -2.4, with the femoral neck returning a score of -2.5 (male reference values) (Figure 1a).

Therapy with estradiol in transdermal application (25-50 µg/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 estradiol, values in our target range were not achieved until 2019. Often, they remained below the detection limit. This best explained by fluctuations in patient compliance. However, BMD in our patient did increase by 16.1%, in response to the therapy from December 2017 to May 2019 (Figure 2b+c).

3. 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 1).

![Figure 1. X-ray of a patient with aromatase deficiency: (A) left hand before and (B) after therapy with estrogen; thick arrows label fractures, thin arrows label some unclosed epiphyseal plates.](http://www.acmcasereport.com/)
<table>
<thead>
<tr>
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<th>Age of patient</th>
<th>Mutation</th>
<th>Hormone profile</th>
<th>Effects on the mother</th>
<th>Influence on the skeletal system</th>
<th>Clinical effects</th>
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<tbody>
<tr>
<td>Baykan et al. 2013 Case report [22]</td>
<td>27</td>
<td>Point mutation</td>
<td>LH und FSH ↑</td>
<td>No virilization</td>
<td>Tall stature</td>
<td>Hepatosteatosis</td>
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<td></td>
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<td>T normal</td>
<td></td>
<td>Open epiphyseal joints</td>
<td>Normal testicular volume and sperm count</td>
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<td>E2 not measurable</td>
<td></td>
<td>Rejuvenated bone age (15)</td>
<td>Slightly reduced sperm motility</td>
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<td>Total cholesterol and triglycerides elevated</td>
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<td>Osteopenia/ Osteoporosis</td>
<td>Ambiguous genitalia</td>
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<td>Low HDL</td>
<td></td>
<td>Recurrent bone fractures</td>
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<td></td>
<td></td>
<td></td>
<td>BMI 25.7</td>
<td></td>
<td>Bone pain</td>
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<tr>
<td>Bouchoucha et al. 2014 [1] 1-6 years old</td>
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<td>Point mutation ⇨ reduced activity of aromatase enzyme</td>
<td>Normal hormone levels</td>
<td>No data</td>
<td>No data</td>
<td>Hypospadias and bilateral cryptorchidia</td>
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<td>FSH, LH, T, AMH und Inhibin B normal</td>
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<td>Normal male external genitalia with descended testes</td>
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<td>Bouillon et al. 2004 Case report [23]</td>
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<td>Frameshift mutation, ⇨ shortened protein</td>
<td>Serum T + free T ↑</td>
<td>No Virilization</td>
<td>Tall stature</td>
<td>Normal testicular volume</td>
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<td></td>
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<td></td>
<td>LH and FSH upper normal range</td>
<td></td>
<td>Open epiphyseal joints</td>
<td>Congenital hearing deficit (85% hearing loss)</td>
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<td>E2 not measurable</td>
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<td>Rejuvenated bone age (12)</td>
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<td>Serum estron low</td>
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<td>Low BMD</td>
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<td>BMI 27.7</td>
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<td>Carani et al. 1997 Case report [12]</td>
<td>31</td>
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<td>T normal</td>
<td>No virilization</td>
<td>Tall stature</td>
<td>Microorchidism</td>
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<td>0.4% residual activity</td>
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<td>Genu valgum on both sides</td>
<td>Infertility</td>
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<td>Bone pain</td>
<td>Oligospermia with immobile spermatozoa</td>
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<td>Case Report Details</td>
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<td>Laboratory Assessments</td>
<td>Other Observations</td>
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<td>Chen et al. 2015</td>
<td>24</td>
<td>Compound heterozygous point mutation ⇝ reduced aromatase activity</td>
<td>LH, FSH and T normal</td>
<td>No virilization, Tall stature, Testicular size, sperm count, and viability normal</td>
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<td>Deladoëy et al. 1997</td>
<td>Child</td>
<td>Base pair deletion in CYP 19 gene</td>
<td>Free serum T normal, Virilization</td>
<td>No data, Normal testicular descent</td>
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<td>Hermann et al. 2002</td>
<td>27</td>
<td>Frameshift mutation ⇝ stop code</td>
<td>T, androstenedione and FSH↑</td>
<td>Virilization, Tall stature, Oligospermia with reduced sperm motility</td>
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</table>

**Laboratory Assessments:**
- **E2 not measurable**
- **Dyslipidaemia**
- **Insulin and glucose normal**
- **BMI 27.6**
- **Open metacarpal and phalangeal epiphyseal joints**
- **Rejuvenated bone age (14.8)**
- **Hypospermatogenesis and sperm-cell arrest**
- **BMI 30.9**
- **Pectus carniatus**
- **Kyphoscoliosis**

**Other Observations:**
- **Tall stature**
- **Genu valgum**
- **Open epiphyseal joints**
- **Osteopenia**
- **Low BMD**
- **Rejuvenated bone age (16-18)**
- **Normal morphology and vitality of spermatozoa**
- **High linear growth**
- **Normal testicular volume**
- **Low BMD**

**Notes:**
- Compound heterozygous point mutation leads to reduced aromatase activity.
- Base pair deletion in CYP 19 gene results in truncated, inactive protein.
- Frameshift mutation leads to truncated protein and stop code.
- LH, FSH and T normal indicate normal levels of these hormones.
- Free serum T normal suggests normal levels of testosterone.
- No virilization observed.
- Virilization and tall stature observed.
- Oligospermia with reduced sperm motility reported.
- Normal testicular volume confirmed.
- Low BMD detected.
- Kyphoscoliosis and Pectus carniatus noted.
<table>
<thead>
<tr>
<th>Case Report</th>
<th>Compound heterozygous point mutation ⇒ truncated inactive protein</th>
<th>FSH ↑</th>
<th>No virilization</th>
<th>Tall stature</th>
<th>Normal testicular volume and sperm count</th>
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<tbody>
<tr>
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<td>Genu valgum</td>
<td>Cryptorchidism on the right testis</td>
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<td>High fasting insulin</td>
<td>Osteopenia</td>
<td>Fat liver</td>
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<td>Insulin resistance</td>
<td>Low BMD</td>
<td>Acanthosis nigricans</td>
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<td>Dyslipidaemia</td>
<td>Rejuvenated bone age (15.5)</td>
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<td>BMI 29.3</td>
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<tr>
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<td>29</td>
<td>Point mutation</td>
<td>T and LH normal</td>
<td>Tall stature</td>
<td>Bilateral cryptorchidism</td>
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<td>Truncated protein</td>
<td>FSH ↑</td>
<td>Continuing linear growth</td>
<td>Microorchid testis in the inguinal canal</td>
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<td>Diffuse bone pain</td>
<td>Abnormal seminiferous tubules</td>
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<td>Insulin upper normal range</td>
<td>Genu valgum</td>
<td>Atrophied and degenerated epithelium</td>
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<td>Glucose normal</td>
<td>Open metacarpal and phalangeal epiphyseal joints</td>
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<td>BMI 25.4</td>
<td>Rejuvenated bone age (15)</td>
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<td>Osteoporosis</td>
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<td>Low BMD</td>
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<td>Acanthosis nigricans</td>
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<td>Maffei et al. 2007 Case report [26]</td>
<td>25</td>
<td>2-point mutations</td>
<td>T and LH normal</td>
<td>Tall stature</td>
<td>Normal testicular volume</td>
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<td></td>
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<td>FSH ↑</td>
<td>Continuing linear growth</td>
<td>Hypospermia</td>
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<td>E2 not measurable</td>
<td>Diffuse bone pain</td>
<td>Acanthosis nigricans</td>
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<td>Hyperinsulinemia</td>
<td>Genu valgum</td>
<td>Hepatomegaly</td>
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<td>Obesity</td>
<td>Open epiphyseal joints</td>
<td>Non-alcoholic fatty liver (NAFL)</td>
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<td>Insulin resistance</td>
<td>Rejuvenated bone age (15.3)</td>
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<tr>
<td>Case Report</td>
<td>Dyslipidemia</td>
<td>Osteopenia/osteoporosis</td>
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<td>Morishima et al. 1995 Case report [27]</td>
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<td>Hyperinsulinism</td>
<td>Virilization</td>
<td>Tall stature</td>
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<tr>
<td>Stumper et al. 2021 Case report and Review</td>
<td>BMI 32.5</td>
<td>Low BMD</td>
<td>Normal sperm count</td>
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</table>

**Miedlich et al. 2016 Review [4]**
- **BMI**: 29.3
- **Point mutation**: Truncated, inactive protein
- **FSH and LH normal**
- **Virilization**
- **Tall stature**
- **Testicular size and libido normal**
- **Bone abnormalities**
- **Moderate acanthosis nigricans**

**Morishima et al. 1995 Case report [27]**
- **24**
- **Point mutation**
- **Hyperinsulinism**
- **Virilization**
- **Tall stature**
- **Macrorchidia**
- **0.2% residual activity**
- **LDL ↑, HDL ↓**
- **Hirsutism and acne**
- **Osteopenia/osteoporosis**
- **Tanner stage 5 pubic hair**
- **T, LH and FSH ↑**
- **Open epiphyseal joints**
- **E2 and E1 ↓**
- **Rejuvenated bone age (14)**
- **Abnormal glucose and lipid metabolism**
- **Low BMD**
- **Dyslipidemia**
- **BMI 32.5**

Stumper et al. 2021 Case report and Review
- **32**
- **Point mutation in intron 9 in homozygous form (CYP19A1 (NM_000103.3):c.1263+1G>T).**
- **LDL normal, HDL ↓**
- **Unknown**
- **Tall stature**
- **Normal sperm count**
- **T, Prolactin, LH and FSH ↑**
- **Continuing linear growth**
- **Testicular size normal**
- **Triglycerides ↑**
- **shaft fracture of the metacarpal bone IV and a proximal phalanx fracture of the middle finger**
- **E2 ↓**
- **Open epiphyseal plates**
- **Cholesterol ↑**
- **Genu valgum**

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3.1. 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 estrogen deficit result in a variable clinical picture [9]. In contrast to females, the disease is not diagnosed at birth in males. The average age on diagnosis in men is approximately 21 years [10, 11]. They usually present to the physician with excessive growth, metabolic disturbances, and unclosed epiphyseal plates [1, 12-14]. To date, only one male patient has had the defect recognized at birth, through expertise and caused by maternal virilization [15].

First signs of the mutation may be detected in the mother already during pregnancy. These suffer from virilization because androgens are no longer aromatized in the placenta. This causes high concentrations of androstenedione and testosterone to enter both the maternal and fetal circulations [15]. 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 [16]. 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 virilization of the mother [17]. During the second half of pregnancy, extremely low (0.8-1.1% of normal) E2 and estriol levels lead to the confirmation of the diagnosis [16]. 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

Figure 2: BMD of the spine of a patient with aromatase deficiency (A) before (December 2017) and (B) after therapy with estradiol for 17 months (May 2019). (C) The increase in bone density is visualized.
arms and an increased proportion of visceral fat [18]. Radiographs often reveal the incomplete or absent closure of the epiphyseal plates, especially in the metacarpal and phalangeal regions [12]. Clinically, the condition genu valgum is also typical [18]. Hypospadias, undescended testes, and micro- as well as macro-or-chidia are also observed [16]. Various degrees of severity of testicular dysfunction have also been described; it is assumed that estrogen deficiency alters testicular development and function in adults [9].

Furthermore, estrogen deficiency results in altered bone homeostasis. Osteopenia and even severe osteoporosis are often observed, as well as a sometimes severely reduced bone mineral density [19]. Figure 2a depicts the bone mineral density of our patient prior to initiating therapy (32-year-old patient with "loss-of-function" aromatase mutation); Figure 2b after 1.5 years of successful therapy. An increase in bone mineral density of 16% is clearly visible within only 1.5 years (Figure 2c).

Estrogen 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 [20].

3.2. Laboratory values

At the metabolic level, we observe an abnormal lipid profile and insulin resistance. One also finds altered levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), and estradiol (E2) [1, 4, 12, 13, 15, 18, 23-27], as portrayed in Figure 3.

The gonadotropins LH and FSH are produced centrally in the adrenal pituitary gland. They are part of the hypothalamic-piti-tary-gonadal (HPG) axis, which induces in males the synthesis of androgens in Leydig cells and the aromatization of these to estrogens in Sertoli cells, among other things [2]. 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 4 portrays the E2 levels in all 13 male patients at the time of diagnosis. In seven patients, the levels were below the detection limit [15, 18, 23-26]. 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 [4, 12, 13, 27].

Figure 3. Number of patients with normal (blue) or elevated (green) testosterone (T), luteinizing 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).

Figure 4. 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).
3.3. Therapy of Estrogen 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 1 depicts the complete closure of the epiphyseal joints in a 32-year-old patient with aromatase mutation after 27 months of treatment with estrogen.

4. Discussion
Estrogens 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. The clinical effects in male patients carrying this mutation are comparable with patients suffering from breast cancer, mainly women, being treated with aromatase inhibitors [6, 7]. The effect on the estrogen synthesis of men with aromatase mutation and patients under treatment with aromatase inhibitors are summarized in figure 5 and 6. In the process of steroid synthesis, the loss of function of the aromatase or the aromatase inhibition treatment leads to blocked estrogen synthesis (figure 5) [6, 7]. 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 estrogen. For the same reason aromatase inhibitors can be used in male children with short stature. The treatment leads to improved height outcomes [28-30].

In both patient groups, males with mutated aromatase and hormone sensitive breast cancer patients under aromatase inhibitor treatment, the positive effects of estrogens on bone are restricted (figure 6) [31-36]. Patients suffering from aromatase loss of function mutations develop severe osteoporosis. Further hallmarks are tall stature and unclosed epiphyseal joints. The treatment with estradiol dissolves the consequences of the disease. In patients undergoing an aromatase inhibitor treatment due to hormone sensitive breast cancer the blockade of estrogen production is of course desired. But as these patients are also at risk of reduced bone density and increased fracture risk, we must care for osteoporosis prophylaxis [6]. Bone density and bone metabolism are evaluated and whenever needed a treatment, with e.g. bisphosphonates, will be started. Having understood the underlying mechanisms of a blocked or like in our case not functioning aromatase, has great impact on the medical decisions in prophylaxis of osteoporosis and fractures.

Figure 5. 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, estrogens concentrations decrease (thick red arrow), androgens concentrations slightly increase (thin red arrows). Progestagens are indicated in yellow, androgens are indicated in blue and estrogens are indicated in pink.

5. Materials and Methods
5.1 Case Report
The described patient was admitted to our practice. 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.

5.2 Search Strategy for Review of 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 University Hospital Berlin.
Figure 6: Estrogens affect bone homeostasis by promoting bone anabolic features while reducing bone catabolic effects. For the latter, Estrogens 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, Estrogens 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. Estrogens 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, Estrogens reduce apoptosis and the osteo 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 κ B; RANK-L, receptor activator of nuclear factor κ B ligand; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha [33 – 37].

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 mutation 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 on-going or unpublished studies that might be of interest to the work. We thus discovered 12 publications that met our criteria.

5.3 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 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 estrogen re-placement 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.

5.4. Data Acquisition and Quality Assessment

The publications were read in detail several times and the data summarized in a table (Table 1).

In addition, only publications that had undergone a peer-review process were selected. We ensured that the Charité statutes for ensuring good scientific practice were followed.

References


