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Screening for hereditary haemochromatosis in patients undergoing knee arthroplasty

A RETROSPECTIVE COHORT STUDY OF 2,035 PATIENTS

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Aims

Hereditary haemochromatosis is a genetic disorder that is caused by several known mutations in the human homeostatic iron regulator protein (*HFE*) gene. Abnormal accumulation of iron causes a joint disease that resembles osteoarthritis (OA), but appears at a relatively younger age and is accompanied by cirrhosis, diabetes, and injury to other organs. Increased serum transferrin saturation and ferritin levels are known markers of haemochromatosis with high positive predictive values.

Methods

We have retrospectively analyzed the iron studies of a cohort of 2,035 patients undergoing knee joint arthroplasty due to OA.

Results

No patients had *HFE* gene C282Y, S65C, or H63D mutations testing. In total, 18 patients (2.96%) of the male cohort and 51 (3.58%) of the female cohort had pathologically increased ferritin levels that may be indicative of haemochromatosis. Seven patients (0.34%) had serum transferrin saturation above 45%.

Conclusion

The awareness for the diagnosis of this disorder in Orthopaedics is low and needs improvement. Osteoarthritic patients undergoing knee arthroplasty should be routinely screened for haemochromatosis by iron studies and referred to genetic testing when needed.
Level of evidence: Level III - Retrospective cohort study.

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Keywords: Hereditary haemochromatosis, Osteoarthritis, Transferrin saturation, Ferritin

Introduction

Hereditary haemochromatosis (HH) is a genetic disorder that is caused by several known mutations in the human homeostatic iron regulator (*HFE*) gene. Abnormal accumulation of iron causes a joint disease that resembles osteoarthritis (OA), but appears at a relatively younger age than degenerative OA, and is accompanied by cirrhosis, diabetes, and skin hyperpigmentation. It is not a rare disorder, as the prevalence of the C282Y homozygous mutation in Western Europe is ~ 0.5%, although not all affected are symptomatic.[1] Phatak et al[2] conducted a prevalence study of HH in the USA. They found that the prevalence of clinically proven and biopsy-proven haemochromatosis combined was 0.54% among White persons.

Arthropathy is frequently the first clinical manifestation of haemochromatosis. In any patient with early onset of OA, iron studies are recommended for screening.[3] In a previous study among HH patients, 32 of 199 individuals had arthroplasty surgery with a total number of 52 joints replaced.[4] The authors concluded that HH is a risk factor for arthroplasty surgery due to severe secondary OA. Kennish et al[5] found that increased ferritin levels are associated with

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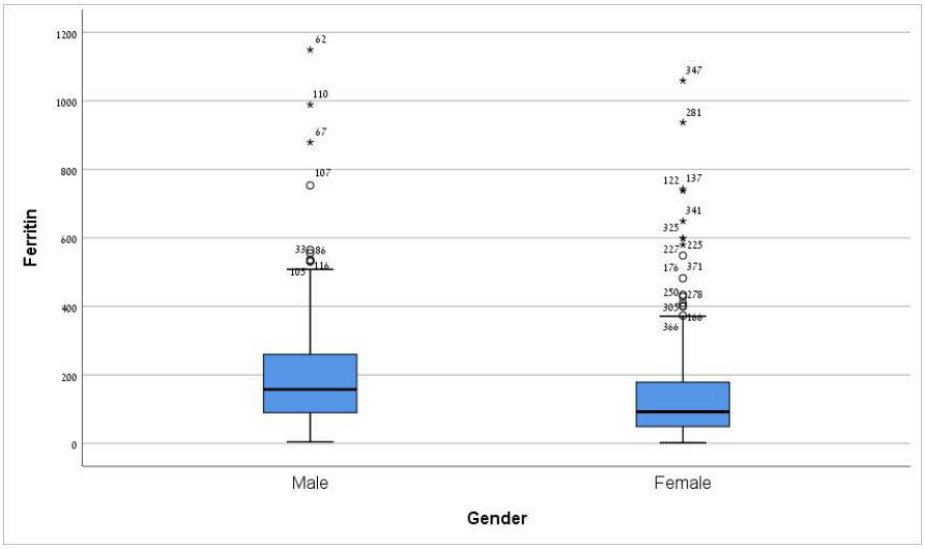

Fig. 1
Ferritin serum levels (ng/ml) distribution in the cohort.

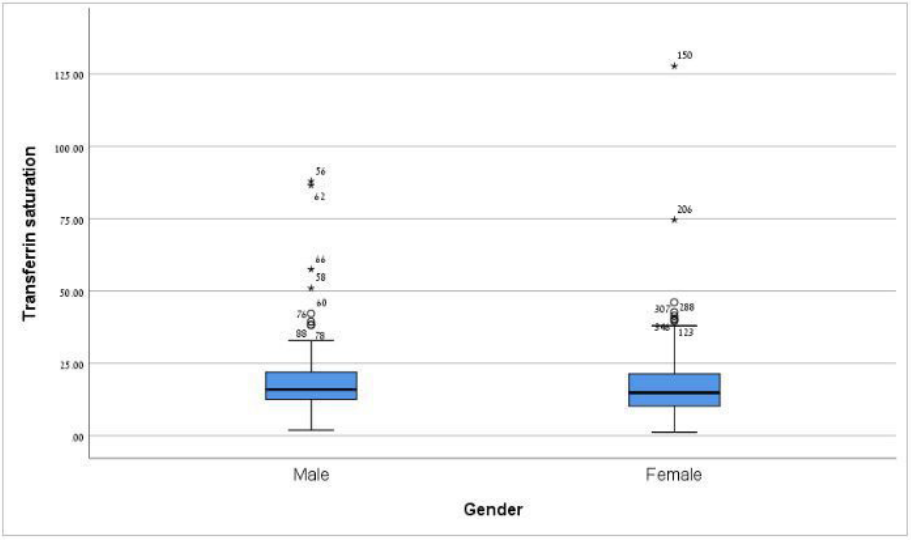

Fig. 2
Transferrin saturation (%) distribution in the cohort.

symptomatic knee OA in males. Elmberg et al[6] found that patients with HH are at increased risk of arthropathies, including the need for arthroplasty surgery. Donnelly et al[7] found that the prevalence of C282Y mutation carriers is significantly higher in patients attending rheumatology and arthroplasty clinics.

Transferrin saturation (TS) is considered to be the best screening test for HH; elevation above 45% is suggestive for HH, before performing expensive genetic tests. Carlsson[8] recommends that when iron saturation level is above 50% or an increased ferritin value is found, genetic testing for HH should be performed. Elevation in ferritin is not specific and can be caused by many disorders such as surgery,[9] inflammation, liver disease, obesity, and alcohol consumption.[10] Bacon et al[11] reported that if serum ferritin levels are > 300 ng/ml in men or > 200 ng/ml in women, 88% and 57% respectively would be C282Y homozygotes.

Table I. Serum ferritin levels (ng/ml) in the cohort.

Sex	Mean (SD)	Range
Male (n = 117)	203.5368 (194.09780)	4.60 to 1,148.80
Female (n = 258)	136.7388 (148.16741)	1.80 to 1,059.10
Total (n = 375)	157.5797 (166.52648)	1.80 to 1,148.80

SD, standard deviation.

The purpose of this paper is to analyze documented *HFE* gene C282Y, S65C, or H63D mutations testing,

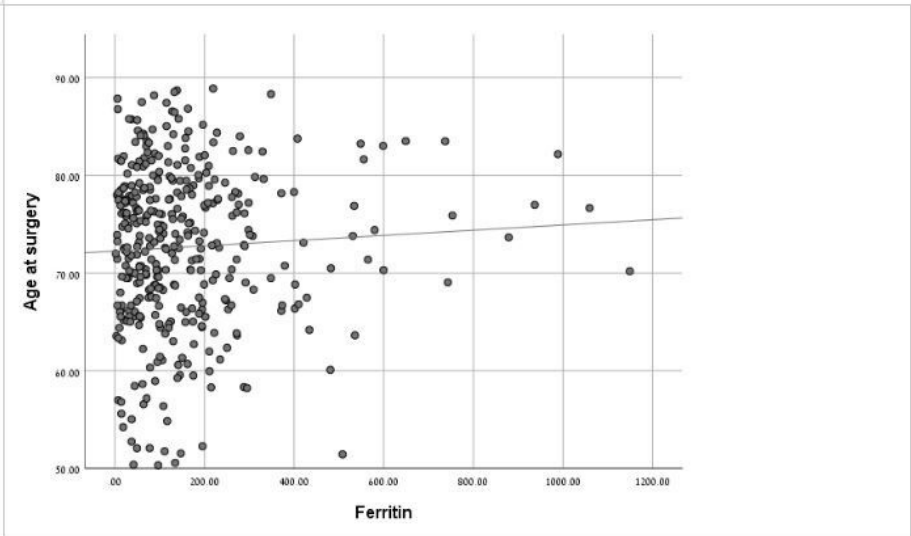

Fig. 3

Linear regression analysis: ferritin serum levels (ng/ml) and age at surgery.

serum ferritin levels, and transferrin saturation in a cohort of patients diagnosed with knee OA who underwent total or partial joint replacement. We will additionally investigate whether there is an increased incidence of elevated levels of ferritin or transferrin saturation, in comparison to the general population, and calculate the risk of HH in this group.

Methods

This retrospective study was approved by our institutional review board and a waiver of informed consent was granted. All medical record data were collected at one tertiary care centre. A computerized search using MDClone software (MDClone, Israel) was performed in our institutional data systems for total and partial knee arthroplasty in patients aged above 50 years. Inclusion criteria were primary partial or total knee arthroplasty for OA. Exclusion criteria were revision arthroplasty, inflammatory arthritis, arthroplasty due to a tumour, and ferritin result up to six weeks after surgery.

Statistical analysis. Independent-samples *t*-test was used to determine whether the sample mean is statistically different from a known population mean after checking for normal distribution (significance defined as $p < 0.05$). The odds ratio (OR), its standard error, and 95% confidence interval (CI) were calculated according to Altman. Statistical analysis was performed using IBM SPSS Statistics version 25 (IBM, USA).

Results

A total of 2,035 patients older than 50 that underwent total or partial knee arthroplasty diagnosed with osteoarthritis were identified in our data system between 2010 and 2020. The mean age at surgery of patients was 71.2 years (standard deviation (SD) 8.2, 50 to 96); 70.1% were female (1,427). All patients were diagnosed with OA as other indications for knee arthroplasty were excluded.

***HFE* gene.** No patients from the cohort had *HFE* gene C282Y, S65C, or H63D mutations testing, and thus none had a definitive diagnosis of HH.

Ferritin. Valid ferritin data (see exclusion criteria) was available for 117 males (19.21% of the male cohort) and 258 females (18.09% of the female cohort). Mean ferritin levels are summarized in Table I. The mean value was 203.54 ng/ml (SD 194.1) for men and 136.74 ng/ml (SD 148.17) for women. The distribution is shown in Figure 1. In the general population (World Health Organization data), the mean serum ferritin in an age matched group for men is 131 ng/ml and 80.7 ng/ml for women.[12] The differences between our group and the general population are 'very highly' significant; $p < 0.001$ for men (95% CI 36 to 108.8) and $p < 0.001$ (95% CI 37.87 to 74.2) for women.

In total, 18 men had ferritin levels above 300 ng/ml (2.96% of all male patients, 15.39% of men with available iron studies), and 51 women had ferritin levels above 200 ng/ml (3.58% of all women, 19.77% of women with available iron studies). Considering the data published by Bacon et al,[11] the hypothetical calculated prevalence of HH in our whole male cohort would be 2.61% and 13.54% in the group with available iron studies. In the female cohort, it would be 2.04% and 11.27%, respectively. The OR for a male undergoing knee arthroplasty in our group to have HH compared to Phatak et al's[2] study of a white population is 5.1096 (95% CI 2.9434 to 8.8700) and for a female is 3.9312 (95% CI 2.5339 to 6.0988). The OR for a male undergoing knee arthroplasty in the group with available and valid iron studies (see exclusion

criteria) to have HH compared to Phatak et al's[2] study is 29.9997 (95% CI 16.8058 to 53.5518) and for a female is 23.9818 (95% CI 15.2175 to 37.7936).

Transferrin saturation. Transferrin saturation (TS) data were available for 101 males (16.59% of the male cohort) and 212 females (14.87% of the female cohort). The mean value was 19.84% (SD 13.74) for men and 17.26% (SD 12.29) for women. Four male and three female patients had TS above 45% (0.34% of the whole cohort, 3.85% of the males and 1.42% of the females with available TS). Figure 2 shows distribution data. In the USA general population (Centres for Disease Control and Prevention data),[13] the mean TS in an age-matched group is 25.65% for men and 20.95% for women. Mean TS in our cohort is lower than the general population and the differences are 'very highly' significant: $p < 0.001$ (independent-samples *t*-test) for men (95% CI -8.52 to -3.1) and $p < 0.001$ (independent-samples *t*-test) (95% CI -5.35 to -2.01) for women.

Correlation of age at surgery/ferritin. We found a low positive correlation ($r = 0.31$) between ferritin levels and age at the time of surgery using Spearman rank correlation coefficient. Pearson correlation coefficient found a reasonable correlation between those variables ($r = 0.54$) (Figure 3).

Discussion

Once diagnosed, haemochromatosis can be treated by repeated phlebotomies. Its severe irreversible consequences, such as cirrhosis, diabetes, and injury to other organs, are therefore preventable. Repeated phlebotomies can even reverse some of the effects of iron overload such as liver or heart disease, but it does not reverse established endocrine damage. Although the awareness for the diagnosis of this disorder is low in orthopaedics, an orthopaedist may be the first physician to encounter the patient with haemochromatosis due to arthropathy. Identifying those patients, sometimes years before the appearance of cirrhosis and injury to multiple organs by the orthopaedic surgeon, can have rather important implications on public health, especially in geographical areas with a high incidence of haemochromatosis.

Our results show that no patients from our cohort were tested for *HFE* mutations, despite the fact that the test is readily available in our institution. Only seven patients out of 2,035 had transferrin saturation above 45%, while a significant proportion had pathologically increased serum ferritin levels. The mean serum ferritin of our cohort was 'very highly' significantly elevated comparing to age-matched general population. According to the data published by Bacon et al[11] and the hypothesized calculated prevalence, we can expect approximately 45 undiagnosed cases of HH among our cohort. In summary, the awareness for the diagnosis of HH among orthopaedic surgeons needs substantial improvement, and surgeons must heed this potential diagnosis in the workup of a patient with arthropathy.

Contrary to the findings of Kennish et al[5] that elevated serum ferritin is a risk factor for symptomatic knee OA in males, our linear regression analysis of ferritin levels versus age of surgery did not show that an increase in ferritin led to arthroplasty surgery at a younger age. In fact, we found a positive correlation between plasma ferritin levels and age at the time of surgery.

The limitations of our study include selection bias, retrospectively taking patients with existing iron studies, using hospital data that might be taken during acute illness, and not further analyzing *HFE* gene mutations.

Our conclusion is that osteoarthritic patients undergoing knee arthroplasty should be screened for HH by routine iron studies. Patients with transferrin saturation above 45%, males with ferritin above 300 ng/ml and females with ferritin above 200 ng/ml should be recommended for genetic testing and a consultation with a specialist. Early diagnosis and treatment will prevent the severe consequences of this disease.

Take home message

- Osteoarthritic patients undergoing knee arthroplasty should be screened for HH by routine iron studies.
- Patients with transferrin saturation above 45%, males with ferritin above 300 ng/ml, and females with ferritin above 200 ng/ml should be recommended to perform genetic testing and a consultation with a specialist.
- Early diagnosis and treatment will prevent the severe consequences of this disease.

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- S. Morgan: Validation, Writing – review & editing.
- Y. Warschawski: Formal analysis, Validation, Writing – review & editing.

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