

# Are cataracts associated with osteoporosis?

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**Background:** Calcium is considered an important factor in the development of both osteoporosis and cataract. This study evaluated the association between osteoporosis and cataracts.

**Objective:** To evaluate the prevalence of osteoporosis among patients undergoing cataract surgery, and the association between the two.

**Patients and methods:** This was a retrospective observational case-control study, conducted in the Central District of Clalit Health Services (a district of the largest health maintenance organization in Israel). All Clalit members in the district older than 50 years who underwent cataract surgery from 2000 to 2007 (n=12,984) and 25,968 age- and sex-matched controls comprised the sample. Electronic medical records of all patients in the study were reviewed. The main outcome measure was the prevalence of osteoporosis and the odds ratio of having osteoporosis among cataract patients compared with controls.

**Results:** Demographically, 41.8% were men with a mean age of  $68.7 \pm 8.2$  years. A logistic regression model for osteoporosis showed that age, female sex, higher socioeconomic class, smoking, chronic renal failure, hyperthyroidism, rheumatoid arthritis, inflammatory bowel diseases, and cataract are all associated with increased prevalence of osteoporosis. Obesity is a protective factor for osteoporosis. In all age-groups, osteoporosis was more prevalent in cataract patients than in the control group.

**Conclusion:** Among other well-known risk factors, osteoporosis is associated with the presence of cataracts. Common pathophysiological associations with both conditions, such as calcium imbalance, hormonal abnormalities, and shared genetic predisposition, are discussed.

**Keywords:** cataract, osteoporosis, risk factors

## Introduction

Epidemiologic studies on cataracts have suggested that it is a multifactorial condition with many risk factors.<sup>1</sup> Research has recently highlighted the role of electrolyte imbalance in the development of cataracts. Calcium is of particular concern. Changes in calcium concentration might be an important factor in the development of cataracts.<sup>2</sup> This cation is essential for various lens-fiber cell-metabolism processes.<sup>3</sup> Proper calcium homeostasis is critical to lens clarity. Elevated calcium levels are related to numerous processes that contribute to alterations in the molecular structure of the lens and increased light scattering by the lens.<sup>4</sup> It has been shown that lens calcium content correlates with opacity in cataractous human lenses.<sup>5</sup>

Calcium is also considered an important factor in the development of osteoporosis. Osteoporosis is known to be linked to calcium imbalance, even though serum calcium levels are usually normal in this condition. Various clinical conditions associated

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with abnormal calcium levels result in osteoporosis.<sup>6</sup> The present study evaluated the prevalence of osteoporosis among 12,984 patients undergoing cataract surgery and the possible link between these conditions.

## Patients and methods

The study took place in the Central District of Clalit Health Services health maintenance organization (HMO), a district of the largest HMO in Israel. The electronic medical records of all members aged 50 years and older who underwent cataract surgery from January 1, 2000 and who did not terminate their membership before December 31, 2007 were included (n=12,984). Cataract patients who died or left the HMO during the study period (n=2,251) were excluded.

Osteoporosis was defined by the International Classification of Diseases (ICD)-9 code for osteoporosis, a pathological fracture, a dual-energy X-ray absorptiometry report, or the use of osteoporosis medications. For each cataract patient in the study group, two members of the HMO who were matched in age and sex and did not undergo cataract surgery (n=25,968) were randomly selected from all members of the HMO who were members of the HMO on January 1, 2000 and did not discontinue membership (for any reason, including death) before December 31, 2007. Data extracted on each patient included age, sex, marital status, socioeconomic class (low or other), area of living (rural or urban), and chronic diseases, being smoking, obesity, chronic renal failure, hyperthyroidism, rheumatoid arthritis, and inflammatory bowel diseases.

The study was approved by the institutional review board of Clalit Health Services. Informed consent was not required.

## Observation procedures

The Clalit Health Services HMO maintains a chronic disease registry database, which includes information collected from a variety of sources, including primary care physician reports, medication-use files, hospitalization records, and outpatient clinic records. The methods of registry acquisition and maintenance have been described elsewhere.<sup>7</sup>

## Statistical analysis

Univariate comparison of dependent and independent variables was conducted by chi-square test or one-way analysis of variance, as appropriate. Adjustment for age and sex was carried out. Multivariate logistic regression models were used to estimate the independent (adjusted) effect of independent variables in the model. The threshold for significance was  $P < 0.05$ .

The data were analyzed using the SPSS statistical package (version 12; IBM, Armonk, NY, USA).

## Results

A total of 12,984 patients who underwent cataract surgery during the study period were eligible. We examined various risk factors for osteoporosis for those patients and compared them to an age- and sex-matched control group from the population of the district (n=25,968).

Demographically, 41.8% were men. The mean age in both the cataract and the control groups was  $68.7 \pm 8.2$  years. No difference was found in other factors, including marital status, socioeconomic class, and living place, between the study and control groups (Table 1). Table 2 presents a comparison of diseases associated with risk of osteoporosis between the cataract and control groups.

We further performed a logistic regression model to evaluate the risk for osteoporosis (included in the model sociodemographic and clinical background). Age, female sex, higher socioeconomic class, smoking, chronic renal failure, hyperthyroidism, rheumatoid arthritis, inflammatory bowel diseases, and cataract were all associated with increased prevalence of osteoporosis. Obesity was found to be a protective factor for osteoporosis (Table 3). Men had a significantly higher incidence of osteoporosis with cataract in patients 75 years of age and older.

## Discussion

We found a significant association between cataract and osteoporosis among women of all age-groups and in men older than 75 years. Smoking,<sup>8</sup> obesity,<sup>9</sup> chronic renal failure,<sup>10</sup> hyperthyroidism,<sup>11</sup> rheumatoid arthritis,<sup>12</sup> inflammatory bowel diseases<sup>13</sup> are well known to be associated with osteoporosis and have been reported on extensively. Obesity as a protective factor has already been reported.<sup>14</sup> To the best of our knowledge, this is the first study to show this association.

**Table 1** Comparison of demographics among patients undergoing cataract surgery versus controls

	Cataract surgery patients (n=12,984)	Matched controls (n=25,968)	P-value
Age, years	68.7 ± 8.2	68.7 ± 8.2	1.0
Males	5,423 (41.77%)	10,846 (41.77%)	0.99
Married	7,253 (55.9%)	14,246 (54.9%)	0.06
Low socioeconomic class	4,733 (36.4%)	9,428 (36.3%)	0.85
Living in rural settlements	1,898 (14.6%)	3,731 (14.4%)	0.61

**Table 2** Comparison of diseases and chronic conditions associated with osteoporosis among patients undergoing cataract surgery versus controls

	Cataract surgery patients (n=12,984)	Matched controls (n=25,968)	OR (95% CI)
Smoking	18.6%	15.2%	1.28 (1.21–1.38)
Obesity	24.3%	21.2%	1.20 (1.13–1.25)
Chronic renal failure	11.9%	9.1%	1.34 (1.25–1.44)
Hyperthyroidism	1.7%	1.5%	1.12 (0.95–1.33)
Rheumatoid arthritis	1.6%	1.1%	1.46 (1.22–1.74)
Inflammatory bowel diseases	0.6%	0.5%	1.21 (0.89–1.66)

**Abbreviations:** OR, odds ratio; CI, confidence interval.

This section focuses on calcium imbalance as a common key event, hormonal abnormalities associated with both conditions, and shared ultrastructural abnormalities found in cataract and osteoporosis.

## Calcium imbalance

Osteoporosis is a complex multifactorial disorder characterized by bone fragility and reduced bone quality. The current study provides evidence for the association between osteoporosis and cataract. However, the role of calcium in both conditions is complex. Both cataract and osteoporosis are associated with an imbalance in calcium, not necessarily detectable by simple calcium serum-level testing. Calcium is the most abundant mineral in the body. Over 99% of total body calcium is found in bone and teeth. A constant exchange exists between the calcium held in the bones and circulating calcium. Bone calcium can remain fairly consistent, with calcium being reabsorbed from the bone and deposited at

**Table 3** Logistic regression model for odds ratio for osteoporosis (included in the model sociodemographic and clinical background)

Risk factors and sociodemographics	OR (95% CI)	P-value
Age (for each year)	1.018 (1.015–1.022)	<0.001
Sex (female > male)	18.87 (17.10–20.81)	<0.001
Socioeconomic class (high > low)	1.47 (1.39–1.56)	<0.001
Smoking	1.24 (1.13–1.35)	<0.001
Obesity	0.71 (0.67–0.76)	<0.001
Chronic renal failure	1.08 (0.98–1.20)	0.12
Hyperthyroidism	1.35 (1.11–1.63)	0.002
Rheumatoid arthritis	2.44 (2.01–2.97)	<0.001
Inflammatory bowel diseases	1.28 (0.91–1.82)	0.16
Cataract	1.30 (1.23–1.37)	<0.001

**Abbreviations:** OR, odds ratio; CI, confidence interval.

similar rates. However, when blood serum calcium levels are constantly low, the body reabsorbs calcium into the blood from the bone faster than it can be deposited back, resulting in a loss of bone mass – osteoporosis.<sup>15</sup>

Although less than 1% of body calcium circulates in the blood, that level has vitally important roles in muscle contraction, nerve-impulse transmission, blood clotting, and cell metabolism. A calcium deficiency or difficulty with calcium absorption, even for short periods of time, can result in significant bone loss. This explains why elevated serum calcium levels frequently indicate a deficiency in total calcium. In osteoporosis, blood calcium levels are normal.<sup>6</sup>

The total blood calcium concentration is approximately 150 times greater than that of free calcium in human lenses, as determined by electrodes.<sup>16</sup> It is also twice as high as the calcium concentration in the aqueous humor. These differences suggest that calcium is either sequestered in intracellular compartments, bound to extracellular components of the lens, or both.

Calcium has long been known to play a role in cataract formation. It is essential for various lens-fiber cell processes, including differentiation.<sup>17</sup> Calcium homeostasis is critical to the clarity of the lens,<sup>18</sup> and abnormal calcium content correlates with opacity in cataractous human lenses.<sup>5</sup> Alterations in calcium homeostasis of the lens, which result in increased cytosolic calcium levels, might be an important factor in cataract formation, particularly cortical cataract, posterior subcapsular opacification, and even for the contraction of the lens capsule after cataract surgery.<sup>2</sup>

A decrease in external calcium causes lens swelling and opacification both *in vitro*<sup>19</sup> and *in vivo*,<sup>20</sup> while an increase in internal calcium is a feature of most cataractous lenses. The total calcium in human lenses with cortical cataracts was found to be four times higher than that in clear lenses.<sup>4</sup> On the basis of multiple studies that compared clear and cataractous lenses, total calcium was found to be elevated in almost all cataracts by an average of 200%–300%. Even pure nuclear cataracts have two to 26 times more total calcium than do clear lenses.<sup>4</sup>

Elevated calcium levels are related to numerous processes, including activation of proteases;<sup>21</sup> inhibition of Na/K-adenosine triphosphatase (ATPase) activity,<sup>5</sup> cell growth, protein synthesis, and calcium influx; disintegrative globulization;<sup>22</sup> cell death; increased membrane permeability; and aggregation of proteins and lipids.<sup>23</sup> All these factors could contribute to alterations in the molecular structure of the lens and increased light scattering by the lens.<sup>4</sup>

## Hormonal abnormalities associated with both osteoporosis and cataract

Steroids represent one of the most studied endogenous or exogenous substances responsible for both osteoporosis and cataract. Several mechanisms have been proposed for steroid-induced posterior subcapsular cataracts, such as Na/K-ATPase inactivation, oxidative free radical damage, proteolysis, and inadequate energy production.<sup>24</sup> Steroid-induced osteoporosis is the most frequent cause of secondary osteoporosis.<sup>25</sup> Osteoporosis occurs eventually in up to 50% of patients on long-term steroid therapy.

## Genetic predisposition for osteoporosis and cataract

Differences in bone mineral density between individuals of the same age are largely attributable to genetic differences, not differences in environmental exposure.<sup>3</sup> Remarkably, several of the genes thought to play a role in osteoporosis were recently targeted as possibly being linked to cataract development.<sup>26</sup>

## Intercellular matrix

Collagen is a central component of the organic bone matrix, and has been discovered to be an essential component of the lens extracellular matrix (ECM).<sup>27</sup> Some subtypes of collagen are suspected of being involved in the pathogenesis of osteoporosis, and were also demonstrated in the human lens: types I, IV,<sup>28</sup> IX, and XVIII.<sup>27</sup> Other components of the ECM, such as laminin<sup>29</sup> and fibronectin,<sup>30</sup> were found to be essential in both bone and lens function.

## Local transcellular level

A multitude of cytokines, prostaglandins, and local growth factors were shown to be responsible for the communication between cells in the bone as well as in the lens, and incriminated in the pathology of osteoporosis and cataract, respectively.<sup>31</sup> The list includes epithelial growth factor, fibroblast growth factor, transforming growth factor,<sup>29</sup> the insulin-like growth-factor system, interleukins (ILs), particularly IL-1 and IL-6, tumor-necrosis factor alpha, and prostaglandin E<sub>2</sub>.<sup>32</sup> Studies have been conducted over two decades on the regulatory role of nitric oxide in bone metabolism,<sup>33</sup> but only recently was this short-living agent demonstrated to be critical in lens epithelial cell processes.<sup>34</sup>

## Cellular level

Polymorphism in the hormonal receptors could be a common source for osteoporosis and cataract. Vitamin D-receptor or

estrogen-receptor<sup>35</sup> genes are good candidates. *LRP5*, coding for the lipoprotein receptor-related protein 5,<sup>36</sup> should be highlighted too. Although the implication of gene polymorphism concerning bone morphogenetic protein 2 involved in the regulation of osteoblast differentiation is still controversial in osteoporosis pathogenesis, this protein was shown to be crucial in proper lens function.<sup>37</sup>

The strength of the current study is that it was based on a large community population. Potential limitations of our study must also be considered. Although detailed information on a multitude of potential confounders was collected and adjusted for, the authors cannot rule out the possibility that unmeasured confounders may explain the observed association.

In retrospect, there are inherent limitations to the study. This case-control study was based on the assumption that patients not undergoing cataract surgery do not have cataract. It is possible that some patients had cataract that had no clinical effect or did not undergo surgery for other reasons. This may have been a potential confounder. However, as the study population was relatively homogeneous, we believe that the results were not influenced significantly.

We selected controls that did not have cataract surgery. We did not want to limit the controls to HMO members who visited an eye clinic, since this might have introduced other ocular pathologies into the control group and led to various biases. However, because the accessibility to health services in Israel in general and in this district in particular is quite high, we assume that if the control patients had a visually significant cataract, they would have seen an ophthalmologist and been referred for cataract surgery.

Another potential limitation is that osteoporosis could have been diagnosed prior to the cataract surgery. There was no information on cataract subtypes in our study. Lens opacity can exist without symptoms, but is clinically relevant only if visual function is considerably decreased,<sup>38</sup> requiring surgery. We included all cases requiring lens extraction. In the Israeli health care system, all patients in the study had the same access to cataract extraction. However, we cannot exclude potential bias because of the underestimation of cataract prevalence, which would lead to diluted risk estimates.<sup>38</sup>

In conclusion, in a large cohort of 12,984 cataract patients undergoing cataract surgery and 25,968 controls, osteoporosis was significantly more prevalent among cataract patients. As so many epidemiologic risk factors for cataract have been identified, and currently there are no tested strategies for the primary prevention of cataract in the community,<sup>39</sup>

we suggest that future cataract research focus on the primary prevention of cataract. This may be achieved by performing more complex study designs looking at multiple factors that contribute to a single mechanism of cataractogenesis.<sup>40</sup> The need to standardize exposure and outcome measurements will become more important as clinicians seek to better synthesize data from multiple studies.

## Disclosure

The authors report no conflicts of interest in this work.

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