# Osteoporosis: A Future Public Health Problem for Israel? Medical and Legal Obligations

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**ABSTRACT:** Starvation in early life can lead to premature metabolic syndrome and bone demineralization. Osteoporosis in the Jewish population may not yet be a recognized syndrome, but the harsh conditions to which Holocaust survivors were exposed may have increased the incidence of the condition. Immigrants and refugees who came to Israel from East Africa and Yemen – whether decades ago or more recently – may have been at increased risk of undernutrition during pregnancy, affecting both the mother and consequently the offspring. This malnutrition may be further exacerbated by rapid overfeeding in the adopted developed country. This problem was also recognized at the turn of the 21st century in poor and underdeveloped countries and is becoming a global public health issue. In this review, the risks for premature metabolic syndrome and bone demineralization are enumerated and preventive measures outlined.

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**KEY WORDS:** early-life starvation, bone metabolic syndrome, Holocaust survivors

In 2015–2016 we witnessed an unprecedented wave of human migration from underdeveloped and poor countries in the Middle East, North Africa, and Central and South America to northern European countries and North America.

Even before the establishment of the State in 1948, Israel accepted Jewish immigrants from East Africa and Yemen who were fleeing from hunger and war, seeking reunification with the Jewish people, or wishing to build a better life. As a result of that migration and the conditions from which these immigrants fled, it is expected that within the first few decades of their life their medical and social demands will exert a significant strain on Israel's public health resources. Health officials can apply what they learned from their experience treating medical conditions specific to Holocaust survivors.

Some of the immediate effects of starvation on humans emerged over 17 months in the early 1940s from the clandestine studies performed by the Warsaw Ghetto Medical School [1,2]. The Warsaw Ghetto study noted multiple effects of malnutrition on children, particularly their metabolism and endocrine functions. Their bone histology showed signs of hunger osteopathy, architectural and matrix changes (namely osteoporosis), and osteomalacia. Since bone healing did not occur, surgical fixation was not possible [1].

The long-term effects of malnutrition on human development have been known for some time. However, they were examined scientifically only late in the 20th century [3]. Based on those results, a different approach to the epidemiology of hunger disease was implemented [4-6]. The impact of early-life malnutrition on the development of adult diseases was discovered some 40 to 50 years after exposure to hunger in World War II during the embryonic, fetal, neonatal or childhood periods of the affected populations [7,8].

The historical background to the theory that proper early-life nutrition forestalls adult disease was published previously. In brief, during the Second World War, starvation was used by the German authorities as a weapon of suppression and punishment, as in Leningrad and the Netherlands. Starvation also occurred in the Channel Islands in 1944 when the food supply was cut off by the Allied invasion of Normandy. More recent examples of starvation include Biafra (Africa) during its civil war [7].

During the Siege of Leningrad, the German army surrounded the city of 2.9 million people (0.5 million children) between September 1941 and January 1944, causing 830,000 deaths [8]. Forty years later, Sweden's Karolinska Institute studied the child survivors in adulthood. Their mothers had been pregnant during the siege and the study subjects had been born either during the siege or later. The mothers' sustenance consisted of only 300–800 daily calories during their pregnancy. The study found a direct correlation between gestational deprivation and the onset of cardiovascular disease in adulthood [9,10]. The exact number of Jews who lived through this siege was not recorded.

In November 1944 the occupying German forces instituted an embargo on Holland in response to interference with vital railway lines. This embargo led to a severe food shortage in the densely populated western Netherlands. The caloric supply was gradually reduced to 1000, then to 800, and by April 1945 to 400 calories a day. The Dutch registry recorded some 18,000 deaths related directly (and several thousand indirectly) to the famine. In the 1980s, researchers at the University of

Amsterdam studied the records of those born during the embargo. The study found that the children born during this time were small in size and had a low birth weight, and that in later years were predisposed to metabolic aberration (glucose and lipids) and obesity and had an increased mortality rate by the age of 50. This cohort was compared to children born in the non-affected eastern Netherlands, which was found to suffer a decline in reproductive function, early menopause, and increased incidence of breast and colon cancer [11-13]. This group also included approximately 1500 Jews hiding in Holland during the siege who were also likely exposed to nutritional deprivation.

In the Channel Islands off the coast of Normandy, the famine affected 60,000 residents. A 5 year period of German repression followed until early 1945. The 1944 invasion of Normandy bypassed the islands. The food supply to the islands from the continent was cut and by the end of 1944 and early 1945 the shortage became critical [14,15]. Just prior to the invasion, women, children and the Jewish population were all evacuated to the British mainland. Three Jewish women married to non-Jews were betrayed and deported to Auschwitz, but they survived.

Starvation affected the islanders as well as the occupiers. The health consequences were studied in those born just before the war and were compared with a cohort evacuated to England. The islanders were found to have cardiovascular morbidity, delayed puberty, and increased rates of breast cancer (although statistically not significant).

The late effects of early-life starvation were assessed in a large peacetime population in England and Wales, and the hypothesis of the effects of early life nutrition on the development of adult diseases was confirmed [15-17].

These comprehensive studies initially investigated the pediatric population and the nutrition of the developing human. In the 1980s, this research was extended to adults [15]. By 1992, these studies confirmed the theory that metabolic syndromes result from starvation and that early-life nutrition determines the extent of disease development in adults [16,17]. Later, epidemiological studies identified the same mechanism of pathogenesis [4,5].

The widely accepted "Baker theory" presents a detailed explanation of the readjustment in intrauterine life by a thrifty modulation of physiology, by "reprinting," that is, by a "programming" mechanism [17,18].

Later studies, unrelated to the Second World War, found a predisposition to, and development of, metabolic disease in the Nauru population after the island had become economically independent. The mineral boom in the country in the 1960s and 1970s led to a "westernization" of the diet, and the Micronesian islanders rapidly developed obesity and diabetes [6]. A more recent Swedish study of the population of Biafra, conducted some 40 years after the civil war and subsequent starvation caused by the total blockade of the region, found the same metabolic results [7].

In these studies, the mechanisms of metabolic changes were re-assessed. Jews were not studied as a separate group and therefore the importance of these studies lies only in the re-affirmation of the programming mechanism.

The findings of long-term effects of starvation in early life have been reproduced experimentally in various animal species, in different geographic areas, and by different researchers. It is appropriate to recall the conclusions of Nobel Laureates Paul Ehrlich and Robert Koch at the end of the 19th and beginning of the 20th centuries. According to their hypothesis, the mechanism of a disease is not disputable once it has been experimentally reproduced.

None of these studies dealt with bone mineral metabolism. The theory of fetal programming of musculoskeletal pathology (adipose tissue, sarcopenia, osteopenia) was developed somewhat later than the metabolic and oncologic aspects but was eventually accepted globally.

There is now a plethora of publications supporting the theory that early-life malnutrition predisposes adults to osteoporosis [19,20]. In 2000, Cooper et al. [21,22] described the pathogenesis of osteoporosis and attributed a role to intrauterine programming. This research confirmed an earlier analysis of growth in infancy and bone mass in adult life. In 2004, osteoporosis was considered to be of developmental origin. This was of great significance for future fracture prevention [23,24].

By 2012, the epigenetic hypothesis of the developmental origin of osteoporosis had been established, as was the effect of Second World War conditions on carcinogenesis [25]. The term "Jewish osteoporosis" has been used to refer to Holocaust survivors living in Israel [26-32].

Marcus and Menczel [26] established that women's bone metabolism was adversely affected by starvation during the Holocaust. In Australia, research on the late effects of nutritional deprivation or prolonged starvation on 15 survivors of the Holocaust was published [3,27]. Although the small sample sizes are insufficient for statistical significance, the individual cases indicate a clear connection between premature adult osteoporosis and deprivation during fetal, postnatal, and early life.

Of great importance are the consequences of the generational transfer of a metabolic insult suffered by those who lived during the war [26,29]. To illustrate one such case are the metabolic changes that occurred in a woman who had been born in a Hungarian ghetto during World War II. She was born with below average body length and her growth was slow. This condition, however, was followed by normal development after the war. She settled in Sydney, and over a period of 50 years developed hyperlipidemia, diabetes (in her forties) and the onset of osteoporosis in her fifties. Her Australian-born son developed hyperlipidemia in his thirties and suffered a myo-

cardial infarction at age 39. His bone densitometry at age 40 already showed a -1.5 DEXA measurement. Table 1 details the impact of starvation on this woman as well as on her adult son, showing a clear generational transfer [3,26,29].

Apart from pure osteoporosis, the risk of a specific pathology could arise and was found in recent Ethiopian immigrants. This disorder, lathyrism, is similar to the pathology found in Jews incarcerated during WWII in the Vapniarka camp.

**Table 1.** Generational transfer: effect of a Holocaust survivor's starvation in her adult son

| | Age in ghetto | Duration of starvation | Lipids | Blood pressure | Diabetes | Osteoporosis + fracture risk (%) within the next 5 / 10 years |
|---|---|---|---|---|---|---|
| **Mother** | Born 1943, ghetto in Hungary<br><br>Treated 1945, in Rothschild Hospital, Vienna | Last trimester of gestation. Mother born premature. Hospitalized for 3 months postnatally | High | High | High | High (13% / 26%) |
| **Son** | Born 1975, Sydney, Australia | Not applicable | High | High | Normal | Low to moderate (0.5% / 1%) |

### EFFECTS OF EATING GRASS PEA OVER AN EXTENDED PERIOD

During World War II Romanian Jews were incarcerated in Transnistria. The starving Jews were offered only grass pea (*Lathyrus sativus*), a plant that grew freely in the Ukrainian desert at the time. The Romanian fascist government deported and either instituted or contributed to the extermination of half of the 800,000-person Jewish community.

Grass pea is harmless to humans in small quantities, but when constituting a major part of the diet for an extended period, it can cause devastating motor neuron disease, neurolathyrism, which is a paralytic syndrome due to spinal cord damage (anterior horn cell death and demyelinization). It can also cause angiolathyrism (i.e., ischemia resulting from peripheral arterial occlusion), resulting in gangrene, amputations, osteolathyrism, osteoporosis, and various deformities as a result of the lack of closure of epiphyseal lines. Bowing can occur due to mitochondria-originating collagen tissue deficiency [33,34].

Close to 1800 detainees interred at Vapniarka suffered from these disorders [35]. In the 1950s, these syndromes were investigated in about 200 survivors at Sourasky Medical Center, Tel Aviv. More recent studies identified the toxic agent, and researchers are attempting to grow a toxin-free plant in the wild to prevent starvation in areas suffering from famine [33].

In contrast to starvation during the Second World War, which led to an increase in osteoporosis in women, syndromes associated with the consumption of grass pea were more prominent in men. This high caloric but toxic legume is grown in Ethiopia, spreading widely in the desert, and is often consumed by starving populations. The Israeli medical system should consider investigating health issues specific to these immigrants in order to provide early diagnosis and palliative care. Such studies will mandate involvement of public health authorities and implementation of certain measures to prevent the late effects on metabolism in a society with a high nutritional supply.

**The risks are fourfold:**

- The primary risk is starvation in utero (total, partial or selective). The effects are trimester-sensitive during gestation, involving a distinct part of the organism. For example, protein and glucose deficiency affects brain development in the first trimester, cortisol and growth hormone deficiency affects bone and internal organs in the second trimester, and restriction of limb and kidney development in the third trimester [3,29]. Screening for diabetes using the HbA1c blood test, as well as screening for deficiencies in lipids (triglycerides, cholesterol with fractions) and minerals (calcium, magnesium, phosphates, and vitamins D and K2) could lead to preventive measures being implemented to combat diabetes, obesity, atherogenesis and bone demineralization in adults. Untreated vitamin K deficiency could lead to catastrophic cerebral hemorrhaging in the embryonic first stage of pregnancy and to the paradoxical reaction of excessive mineralization, known as epiphyseal arterial wall calcifications, and osteoporosis in later stages [29].
- The second risk to the health of immigrants from underdeveloped countries is the sudden compensatory hyperalimentation or overfeeding. This "catch up" could lead to adolescent obesity, early adult glucose and lipid metabolic disturbance, and eventually a full-blown metabolic syndrome, including osteoporosis [24,25,27-29,35]. Prevention requires extensive educational programs on nutrition for immigrants and, equally important, comprehensive dietary management.
- The third risk factor is the rare but existent "lathyric" osteopathy among those fed with cooked grass pea, which is available in the desert or mountainous areas of Ethiopia [31]. Apart from thorough neurological assessment, a simple thrombo-agglutinin test with quinine might assist in diagnosis [32]. Recent magnetic resonance imaging studies conducted in Jerusalem confirmed the localization of the pathology in the spinal cord [36].
- The fourth risk factor in the immigrant population, unrelated to osteopathy but of great importance, is the increased frequency of malignancy in individuals who were starved during their intrauterine or perinatal life, compared to the rest of the population [12,13,15,37].

### CONCLUSIONS

Prevention of the various osteopathies resulting from deficiencies in the nutrition of immigrants from underprivileged countries is a public health issue and a medical and legal obligation. One mineral metabolic disorder in the Jewish population, like

other metabolic disorders, was found to be programmed by conditions from early life, such as intrauterine starvation. The Jewish people represent a particular population that suffered from starvation during the Second World War. Due to the resulting osteoporosis, this group of survivors, especially women, is at significant risk of increased fracture incidence. Within the next three to four decades, the focus must be directed toward the immigrant populations to prevent osteoporosis by means of early diagnosis, immediate treatment, and prophylaxis. Osteopathy in all the previously mentioned forms is a risk that must be evaluated early, since all are preventable and all but lathyrism are curable.

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**"Since Auschwitz we know what man is capable of. And since Hiroshima we know what is at stake"**

Viktor Frankl, author, neurologist and psychiatrist, Holocaust survivor (1905–1997)

**"Most people think that shadows follow, precede or surround beings or objects. The truth is that they also surround words, ideas, desires, deeds, impulses and memories"**

Elie Wiesel (1928–2016), Romanian-born American Jewish writer, professor, political activist, Nobel Laureate and Holocaust survivor. He was the author of 57 books written mostly in French and English