Health-Related Quality of Life and Growth Hormone Treatment

Long-term follow-up studies of women with Turner syndrome and women with osteoporosis

Emily Krantz (née Amundson)

Department of Internal Medicine and Clinical Nutrition
Institute of Medicine
Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

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Cover image: “Growth” Tapestry by Annika Cilke.

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emily.amundson@vgregion.se

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– It does not do to dwell on dreams and forget to live.

J. K. Rowling

ABSTRACT

Introduction Growth Hormone (GH) is used to increase height in Turner Syndrome (TS), the most common sex-chromosome aberration in women. GH is also beneficial for bone mass. However, little is known about how GH treatment affects Health-Related Quality of Life (HRQoL).

Aims To study if previous GH treatment for short stature in TS, and for strengthening bone in postmenopausal osteoporosis, leads to an improved HRQoL and to compare HRQoL to that of women in the general population.

Methods HRQoL was evaluated using questionnaires: The Short Form-36, the Nottingham Health Profile, the Psychological General Well-Being index, and a Self-Rated Health scale (0-100). Women with TS were followed every 5th year for up to 20 years, (n=200, age 16-71 yrs). Women with osteoporosis who participated in a clinical trial of GH treatment for 3 years (n=80, age 50-70 yrs), were followed annually for a total of 10 years. A reference population from the WHO MONICA project, Gothenburg (n=414, 77% women, age 39-78 yrs) was used for comparison and method evaluation of the HRQoL questionnaires.

Results HRQoL in adults with TS was not associated with previous GH treatment in childhood, despite a mean 6 cm taller adult height, during up to 20 years of follow-up. HRQoL was negatively affected by higher age, higher age at TS diagnosis, and hearing impairment but it was similar to that of women in the population. In the women with osteoporosis, HRQoL did not change during the GH treatment or during follow-up despite an increase in bone mineral content ($p<0.01$ vs placebo) and a decrease in fracture incidence from 56% to 28% ($p<0.001$). HRQoL did not differ between the women with osteoporosis and the population. All of the HRQoL questionnaires had acceptable internal consistency (α) when applied in men and women in a population sample. Similar sub-scales correlated strongly ($p<0.01$). All HRQoL questionnaires could differentiate the presence of ill-health ($p<0.01$).

Conclusion Previous GH treatment was not associated with improved HRQoL in the women with TS despite 6 cm taller adult height, nor was GH associated with an improved HRQoL in postmenopausal osteoporosis despite a reduced fracture incidence. HRQoL in both study groups was similar to that of women in the population. The HRQoL questionnaires were reliable and valid.

Keywords: Health-related quality of life, Growth hormone, Turner syndrome, Postmenopausal osteoporosis

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SAMMANFATTNING PÅ SVENSKA

Tillväxthormon (Growth Hormone, GH) erbjuds till flickor med Turners syndrom (TS) under uppväxtåren för att öka deras längd. TS - den vanligaste könskromosomavvikelsen hos kvinnor - förekommer hos ca. 1/2500 födda flickor. TS är inte förenat med brist på GH men leder, i de flesta fall, till kortvuxenhet och bristande äggstocksfunktion. Medfödda hjärtfel, låg ämnesomsättning och benskörhet (osteoporos) är vanligt. Osteoporos, orsakas i regel inte av GH-brist, men man har prövat GH-behandling i syfte att stärka skelettet och minska risken för frakturer i studier. Osteoporos är en folksjukdom och förekomsten i Sverige uppskattas till ca. 20–25% hos kvinnor över 50 år. Att mäta hälso-relaterad livskvalitet är viktigt när man vill utvärdera värdet av en behandling från patientens eget perspektiv.

Syftet var att studera om GH behandling under uppväxtåren för kortvuxenhet vid TS har påverkat den hälso-relaterade livskvaliteten 20–30 år senare hos kvinnor med TS, och om GH behandling i syfte att stärka skelettet leder till en förbättrad hälso-relaterad livskvalitet hos kvinnor med osteoporos. Dessutom studerades livskvaliteten hos dessa grupper i relation till kvinnor i befolkningen. Hälso-relaterad livskvalitet mättes med hjälp av fyra olika, vanligt förkommande, livskvalitetsenkäter, som även jämfördes med varandra.

Inget samband mellan hälso-relaterad livskvalitet och GH-behandling sågs hos de vuxna kvinnorna med TS, trots 6 cm högre längd som vuxen efter upp till 20 års uppföljning. Inget samband fanns mellan livskvalitet och längd i vuxen ålder. Hälso-relaterad livskvalitet påverkades dock negativt av högre ålder, senare diagnos och hörselnedsättning oavsett tidigare behandling. Livskvaliteten hos hela TS gruppen var snarlik den som fanns hos kvinnor i befolkningen. Hos kvinnorna med osteoporos, fanns ingen skillnad i hälso-relaterad livskvalitet under eller efter GH behandlingen. GH behandlingen ökade beninnehållet jämfört med placebo och frakturfrekvensen sjönk från 56% to 28% under 10 års uppföljning. Det fanns ingen skillnad i hälso-relaterad livskvalitet mellan kvinnorna med osteoporos och kvinnorna i befolkningen. Livskvalitetsenkäterna visade en bra samstämmighet hos män och kvinnor i befolkningen.

Sammanfattningsvis: Varken GH behandling eller längd i vuxen ålder var förknippat med en förbättrad hälsorelaterad livskvalitet mätt med enkäter hos kvinnorna med Turners syndrom trots 6 cm längd-ökning efter upp till 20 års uppföljning. GH behandling var inte heller kopplad till bättre livskvalitet hos kvinnor med osteoporos trots förbättrad benmassa och färre frakturer under uppföljningstiden. Livskvaliteten hos båda grupperna var snarlik den hos kvinnor i befolkningen. Livskvalitetsenkäterna stämde väl överens och kunde differentiera mellan hälsa och sjukdom i befolkningsstudien.

LIST OF PUBLICATIONS

This thesis is based on the following studies, hereafter referred to in the text by their Roman numerals (I-IV).

I. **Amundson E**, Wide Boman U, Barrenäs M-L, Bryman I, Landin-Wilhelmsen K.

Impact of Growth Hormone Therapy on Quality of Life in Adults with Turner Syndrome.

J Clin Endocrinol Metab. 2010;95(3):1355-9

II. **Krantz E**, Landin-Wilhelmsen K, Trimpou P, Bryman I, Wide, U.

Health-Related Quality of Life of Adult Women with Turner Syndrome and the Influence of Growth Promoting Therapy: A 20-year Follow-up

J Clin Endocrinol Metab. 2019;104(11):5073-83.

III. **Krantz E**, Trimpou P, Landin-Wilhelmsen K.

Effect of Growth Hormone Treatment on Fractures and Quality of Life in Postmenopausal Osteoporosis: A 10-year Follow-up Study.

J Clin Endocrinol Metab. 2015;100(9):3251-9.

IV. **Krantz, E**, Wide U, Trimpou P, Bryman I, Landin-Wilhelmsen K.

Comparison Between Different Instruments for Measuring Health-Related Quality of life in a Population Sample, the WHO MONICA Project, Gothenburg, Sweden – an Observational, Cross-Sectional Study.

BMJ Open. 2019;9:e024454

TABLE OF CONTENTS

ABBREVIATIONS

BMC	Bone Mineral Content
BMD	Bone Mineral Density
DXA	Dual-energy X-ray Absorptiometry
GH	Growth Hormone
HRQoL	Health-Related Quality of Life
HRT	Hormone Replacement Therapy
IGF-1	Insulin-like Growth Factor-1
MONICA	MONItoring of trends and determinants in CArdiovascular disease
NHP	Nottingham Health Profile
PGWB	Psychological General Well-Being index
PTH	Parathyroid Hormone
QoL	Quality of Life
SF-36	Short Form-36 questionnaire
SHOX	Short-stature Homeobox-containing gene
SRH	Self-Rated Health
TS	Turner Syndrome
WHO	World Health Organization

PROLOGUE

As a medical student, I often found myself wondering (perhaps rather naively) whether treatments that did not obviously cure, ameliorate, or prevent disease were being offered to patients just because they were available. Extensive treatment of the very, very elderly and treatments that seemed primarily cosmetic were especially worrying to me. What was the point? Is it just because we can? If so, that is just not good enough. This led me wonder how the patients felt about it? Do we ask them in a scientifically valid way? And if so, are the results reliable and meaningful?

I wasn't the first to wonder; decades of thinking and work had already been done on developing the concepts surrounding what we call Quality of life (QoL) and Health-related quality of life (HRQoL) – developing, testing, and implementing questionnaires, both general and disease specific, in order to find out. In 2008 the National Health Service in Great Britain declared that patient reported outcomes like QoL should be prioritized as equal to more established endpoints, like mortality, in clinical trials and implemented in clinical practice.

Even so, my impression was that the medical profession wasn't that interested. In our daily practice as physicians it is easy to use objective variables as a surrogate in our thinking for how the patients ought to feel which is not the same as actually asking them.

Thankfully, attitudes toward patient reported outcomes have changed since I was a student. Now they are a standard, and sometimes even a required, element in pharmaceutical trials. I am confident that HRQoL is quantitatively measurable in a way that contributes to our understanding of how a disease and its treatment affect the patients. We *must* ask for the patients' perspective to help us prioritize the abundance of medical treatments and therapies available to us so that we choose treatments that are beneficial both in the traditional objective sense (cure, increase survival, disease prevention) and in a subjective sense.

INTRODUCTION

An evaluation of effectiveness and efficiency is essential when a medication is tested or when a medication's treatment indication is widened.[1] Effectiveness, sometimes called efficacy, relates to whether the treatment in question has the desired effect, first in a study setting and then in clinical practice. Efficiency refers to whether the treatment is "worth it" in relation to the resources it consumes.[2] Efficiency is harder to evaluate and often requires a long-term, multifaceted approach that is not limited to health-economics alone. Patient reported outcomes like HRQoL are also important aspects that should be considered when assessing the efficiency of a treatment.

In the 1980s, recombinant biosynthetic Growth Hormone (GH) became available. Before this, pituitary derived human GH was very scarce and associated with serious risks. This new, unlimited (albeit expensive) supply of GH, has since inspired a widening of GH treatment indications to include not only children and adults with GH deficiency, but also children and adults with conditions that are not associated with GH deficiency.

GH treatment is expensive and cumbersome since it is administered as a daily subcutaneous injection. In the patient categories that are not associated with GH deficiency, it is relevant to ask whether the treatment is effective and efficient, now that we have a few decades of treatment experience behind us. So far, research has been heavily efficacy-focused. But does GH treatment increase QoL, from the perspective of the patients, in those without GH-deficiency?

In this thesis, the association between previous GH treatment and HRQoL in two non-GH deficient patient groups is explored:

- women with Turner Syndrome (TS) who received GH in childhood to increase their height.
- women with postmenopausal osteoporosis who were treated in adulthood to increase bone mass and decrease fracture prevalence.

AIM

The general aim of this thesis was to study whether previous GH treatment for short stature in TS, and for strengthening bone in osteoporosis leads to an improved HRQoL.

Specific aims:

I. To study the impact of previous GH treatment in childhood on HRQoL in women with TS and to compare the HRQoL of women with TS to that of age-matched women in the population. (Paper I)

II. To describe HRQoL in women with TS during up to 20-years of follow-up with a focus on how GH treatment and comorbidity influence HRQoL during adulthood and to compare the HRQoL of women with TS with that of women in the general population. (Paper II)

III. To study whether GH treatment during 3 years or placebo followed by other bone specific treatments for another 7 years (for a total of 10-years follow-up) improved bone mass, fracture prevalence and HRQoL compared with age-matched women in the general population. (Paper III)

IV. To evaluate and compare the psychometric properties and results of three different, widely used, generic HRQoL instruments and a SRH scale in a population sample of men and women of whom the women were used as a reference population in papers I-III. (Paper IV)

The hypotheses were that previous GH treatment in childhood to increase stature in TS led to an improved HRQoL in adulthood and that the increased bone mass achieved with GH led to reduced fracture frequency and increased HRQoL in postmenopausal osteoporosis. Furthermore, that the generic HRQoL instruments used are valid and could differentiate the presence of ill-health.

BACKGROUND

GROWTH HORMONE

Human Growth Hormone (GH) is a pituitary hormone that exerts its biological effects by binding to specific cell membrane receptors that are present throughout the body.[3] GH especially stimulates longitudinal bone growth in the epiphyses of the long bones in childhood. Other effects that persist in adulthood include, but are not limited to, anabolic effects on bone chondrogenesis, and the metabolism of proteins, carbohydrates, and fat. GH is also believed to have an effect on the central nervous system; its effects on appetite, cognitive functions, energy, memory, sleep, and well-being have all received significant attention.[4] The regulation of GH secretion is complex, but two hypothalamic peptides, GH Releasing Hormone and Somatostatin, stimulate and inhibit GH secretion respectively.[5] The physiological secretion of GH is pulsatile during the 24-hour day, is highest during infancy and during puberty, and then decreases during adulthood with age.[6,7]

In 1956, GH was isolated from the human pituitary gland for the first time.[8] During the following thirty years, GH therapy was only offered to children with severe GH deficiency because of its scarcity.[9] But, in 1985, reports of infection with the prion-mediated disease Creutzfeld-Jacob disease in the central nervous system of patients that had been treated back in the 1950s and 60s stopped the use of human cadaveric GH completely worldwide.[10] This safety scare led the US Food and Drug Administration to accelerate the approval of the use of synthetic, or recombinant, human GH (somatotropin) in 1985.[11] In Sweden and the rest of Europe, somatotropin was registered in 1987, and since then, it has been readily available, which led to a rapid expansion of treatment indications to include not only GH deficient children and adults, but also non-GH deficient children to increase growth and adult height (Table 1).[12]

Table 1. Overview of the current treatment indications for recombinant human GH/somatotropin.

Children	**Adults**
GH deficiency	GH deficiency
Turner syndrome	
Prader-Willi syndrome	
SHOX-deficiency	
Noonan syndrome *	
Chronic renal insufficiency	
Small for gestational age without growth catch-up	
Idiopathic short stature*	

*Not currently an approved treatment indication in Sweden.

HEALTH-RELATED QUALITY OF LIFE (HRQOL)

The current definition of health as it was specified in 1948 in the Constitution of the WHO is broadly defined: "Health is a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity." It was ahead of its time, and implies the absence of illness but also emphasizes positive themes such as happiness, mental and social well-being and QoL.[13,14] Measuring QoL is an ever more relevant endeavour as health care treatments are increasingly able to extend the length of life, sometimes at the expense of quality. But a definition of QoL, and how it is best measured, has been the subject of debate and critique spanning decades, and a consensus seems unlikely to emerge.[15-18] This is problematic in an era when QoL outcomes have become an integral part of clinical medical research in all disciplines - and even seen as primary end-points, alongside survival.[19-21]

There is a widespread view that the patient's perspective complements that of clinicians, and provides important information on the effectiveness of health care and treatment.[22] Patients seek symptom relief, reduced disability, and improved QoL, so it makes sense to involve the patients, as they are the ones best able to report on these aspects of their own health.[23] Most people are familiar with the expression "QoL," but it is clear that it takes on different meanings for different people and the meaning varies according to the situation.[24] To even further complicate matters, the terms "QoL" and "HRQoL" are

used interchangeably in the literature without any real stringency or consensus in clarifying the difference between the two.[25] Because of this confusion of concepts, I will now try to specify what I mean by HRQoL in this thesis and how it has been measured, to ensure that the results are meaningful.[24,26] The definition of HRQoL that has been applied in this thesis is:

> The way a disease or disorder, and its consequent therapy, affects a patient's ability to function, as perceived by the patient.[27]

QoL questionnaires, or instruments, are used to quantify different aspects and dimensions of health (or ill-health) into domains like mobility, ability to perform certain activities, emotional state, sensory function, cognition, social function, and pain, to name some.[19] I argue that the measurement of these concepts can only take on the mantle of being *Health-related* QoL when they are applied in the context of a disease or health care.

Measuring HRQoL with Questionnaires

Patient reported outcomes, like HRQoL, cannot be collected directly and objectively like height or blood pressure. There is an inherent element of judgement, or subjectivity, involved when measuring and reporting HRQoL measures from the respondent and investigator alike. The investigator chooses or creates questionnaires that reflect problems or consequences of a disease or treatment that the patient is thought to have. The respondent, in turn, answers the questions according to her interpretation, personality, situation and moral context. Even the wording and response format of each question may influence how it is answered. All of which introduces biases in HRQoL research that can be difficult to overcome both scientifically and philosophically.[14,28] But subjective measures should not be dismissed; they have consistently been shown to be strong correlates of objective health and even as predictors of mortality.[29]

A patient reported outcome instrument must be valid (the test measures what it is intended to measure) and reliable (consistent).[14,30]

QoL questionnaires are often based on qualitative research to support their **content validity** *i.e.* that they contain valid and relevant questions that are understandable to the patients.[31] Qualitative research involves direct communication with patients *e.g.* interviews, focus groups etc. It is perhaps the most appropriate way to collect data that captures the patient's own perspective in relation to a disease or treatment but it is very resource intensive. Questionnaires facilitate the assessment of the patient's perspective on a larger scale and enable quantitative analysis of the results. But without well-grounded content validity, a questionnaire, and its results, will lack relevancy, and will not produce the right information that allows us to deliver optimal and efficient care to patients.[22]

Another hallmark of an instrument's quality is its **reliability** which refers to the consistency of a measure.[14,24] In the context of QoL measurement, two characteristics are especially important: first that the instrument shows stability over time, or *test-retest reliability* (presuming it is not expected to change because of some kind of intervention), and secondly, *internal consistency* which is the consistency of a person's responses across the questions in a multiple-item measure. For example, if there are 5 questions that together make up a domain like "Vitality" or "Physical functioning" then the responses should correlate with one another, as an indication that the questions are all measuring aspects of the same concept. To test whether an instrument is reliable, it must be tested, or validated, in a representative sample of the patient group or population that one wishes to study.

QoL questionnaires are often classified into "generic" or "specific" instruments:

Generic instruments are intended to measure QoL and health status regardless of the illness or condition of the patient or subject. They pose general questions and are often used in epidemiological studies or health surveys of populations because they permit comparisons across disease categories and comparisons with the general population.[14] However, this generality can also be seen as a weakness since generic questionnaires may contain superfluous questions, or may lack sensitivity to the specific concerns of a given group of patients or subjects.[32] Furthermore, many (especially the early instruments) focus on physical impairment, implicitly making the assumption that poorer physical health indicates

poorer QoL. This may not necessarily be the case since different patients/patient groups may react or adapt differently to similar levels of impairment.[24]

Specific instruments, on the other hand, are designed and adapted for a certain disease, type of person, age group or study. They are more often designed for use in clinical settings and are also intended to be sensitive to differences in QoL that arise as a result of disease activity or treatment that generic questionnaires may miss.[14,24]

In this thesis, a quantitative approach was taken when measuring HRQoL in women with TS and in women with osteoporosis. We used generic instruments that contain questions concerning physical and occupational functioning, psychological state, social interaction and somatic sensation in relation to GH treatment and somatic variables. The results in the patient groups were compared to randomly recruited population samples from the general population.

The instruments used in the studies in this thesis are: Nottingham Health Profile (NHP),[33] the Short Form 36 (SF-36),[34] a self-rated health (SRH) scale of health status measured on a "thermometer" from 0-100,[35] and the Psychological General Well-Being index (PGWB).[36] The latter offers an indicator of psychological well-being and distress while the NHP, SF-36 and the SRH scale are intended to measure health status and aspects of health as it relates to activities generally affected by health conditions.[14] Details of each instrument can be found in the next chapter.

TURNER SYNDROME

Turner syndrome (TS) is the most common sex-chromosome aberration in women. It is a genetic disorder that occurs in approximately one in 2,500 - 3,000 live female births.[37-39] Normally, the human genome is made up of 46 chromosomes: 44 autosomes/body chromosomes and 2 sex chromosomes, *i.e.* XX in females and XY in males. A karyotype is a picture of the number and appearance of the chromosomes in the nucleus of a cell, normally for females 46,XX and for males 46,XY. In individuals with TS, the karyotypes include either the complete absence of the second X-chromosome in all or some of the cells in the body, or

a structural change in one or both of the X-chromosomes in all or some cells in the body. The typical karyotype in TS is Monosomy 45,X (Figure 1). Monosomy 45,X is also most common, found in 40-50% of women with TS. Mosaicism (the presence of two or more populations of cells with different genotypes in one individual who has developed from a single fertilized egg) 45,X/46,XX is present in 15-25%. The remaining individuals have mosaicism with either a multiple X in the second cell line, a Y-chromosome, an iso-chromosome, a ring chromosome, a deletion, a translocation, or a Y-fragment.[40,41]

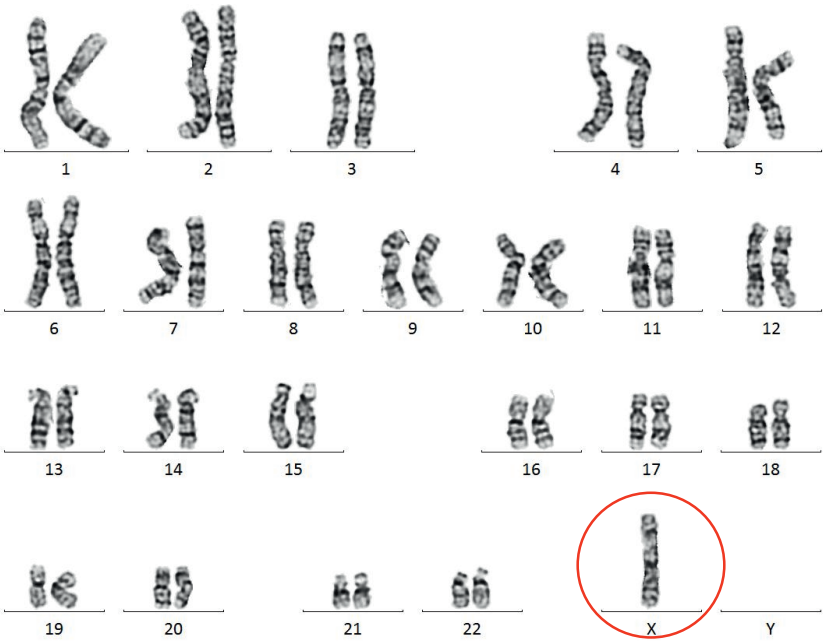

Figure 1. Typical Turner syndrome karyotype: monosomy 45,X. Image courtesy of Dr. Sofia Thunström.

To be diagnosed with TS one must have a combination of one of the typical karyotypes mentioned above, have the physical features of a female (phenotypical female) and have clinical features typical to TS (stigmata), some of which are shown in Figure 2. TS is not known to be hereditary, but there are cases of women with TS giving birth to infants with TS, and of women with a normal karyotype having multiple children with TS.[42]

TS was first described as a disorder affecting girls, associated with short stature, sexual infantilism, and webbing of the neck.[43-45] More recently, the syndrome has come to be associated with a wide range of clinical and psychosocial implications including (but not excluded to): linear growth failure, ovarian insufficiency (resulting in delayed, arrested or even absent pubertal maturation, and infertility), early sensorineural hearing loss, cardiovascular anomalies and an elevated risk for aortic dissection, distinctive congenital skeletal-, digital- and renal anomalies, neurodevelopmental challenges and social anxiety, and a constellation of other disorders that are more common in TS, including hypothyroidism osteoporosis, celiac disease and diabetes mellitus.[38,39,41,46]

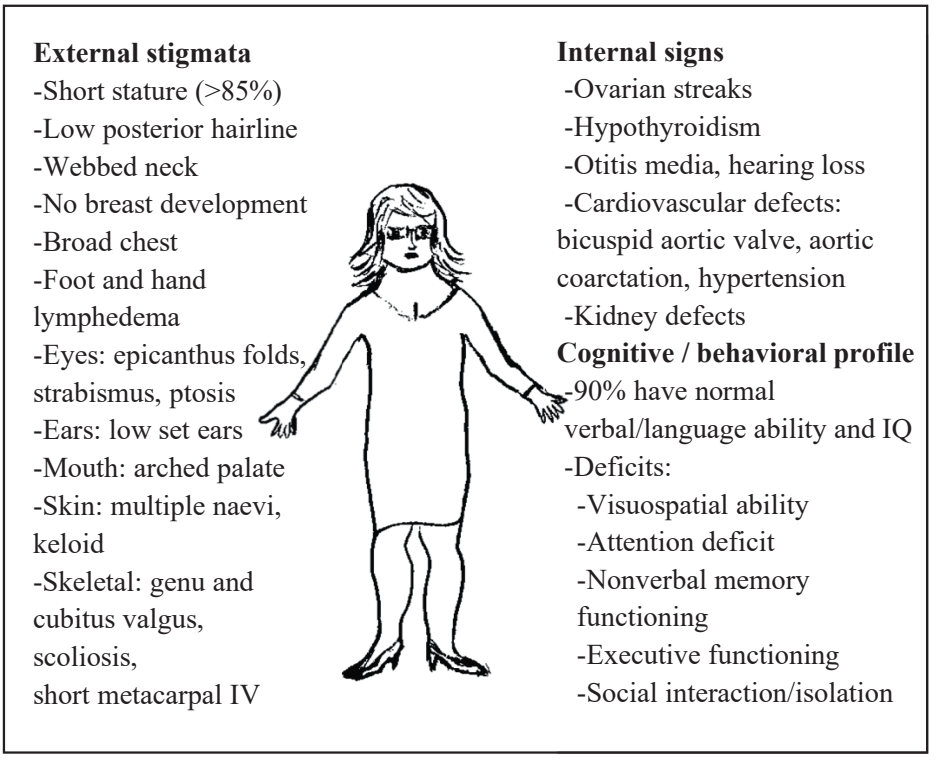

Figure 2. Most common stigmata, signs and cognitive and behavioral profile in girls and women with TS. Illustration by Dr. Kerstin Landin-Wilhelmsen.

The diagnosis is often made in distinct age groups, with peaks during the prenatal period, in infancy and late pre-pubertal period (8–12 years) due to growth failure, during late adolescence due to delayed or absent pubertal development, and during adulthood due to premature menopause or infertility.[47] Early diagnosis is important, since if the problems associated with TS are not addressed, they may result in increased morbidity and reduced QoL.[48,49] (I, II)

It is important to mention that there is a great deal of individual variation in the physical phenotype of the girls and women with TS. The typical phenotype illustrated above affects far from all of the patients, indeed, in some cases, TS is diagnosed even when the typical stigmata are lacking. The same variability is seen in the cognitive and behavioral profile of girls and women with TS. Approximately 10% of TS patients (irrespective of karyotype) have a significant intellectual disability that requires special attention in childhood and into adult life.[39] The majority (approx. 70%) have learning disabilities affecting non-verbal memory, visuospatial ability, perceptual motor cognition, social cognition and/or attention.[46,50,51] However, to quote Ross et al., "difficulties found in most samples of TS females are subtle; most individuals are productive members of their communities."[51] In most studies their education and employment status is equal to, or higher than, comparison groups, but they retire earlier.[52-55] (I,II)

Growth Hormone Treatment in Turner syndrome

The mechanisms behind growth failure in women with TS are not fully understood.[56] Most of the height deficit is believed to be caused by a haploinsufficiency of the Short-stature Homeobox-containing gene (SHOX) on the X chromosome – for normal growth, two copies of the SHOX-gene are needed.[57] TS is not generally associated with a deficiency in the GH - Insulin-like Growth Factor 1 (IGF-1) hormone axis *per se,* but decreased metabolic clearance of endogenous GH, irregular proportions of circulating GH isoforms, and end-organ resistance to IGF-1 have all been suggested as possible contributing explanations to their short stature.[58-60]

GH treatment has nevertheless been used to ameliorate short stature in TS since the late 1980s and there is evidence that GH treatment increases adult height in TS.[61-63] Adult height of untreated girls with TS averages

approximately 143 - 144 cm in North America, Europe and Japan.[64] However, individual studies of adult height in TS have reported means ranging from 137 - 147 cm, with women in Northern Europe at the very top end of that range.[65] Adult height in TS is strongly associated with mean parental height and with normal adult height in their respective country of origin, in addition to there being variability among individuals. In this Gothenburg cohort, the TS women who never received growth promoting therapy in childhood had an average height of approximately 150 cm, ranging between 122 - 165 cm which is 16 cm shorter than a reference population of women from Gothenburg. (II) Compared to a review by Rochiccioli et al who cite a 20-21 cm difference between adult height in GH naïve women with TS and the population in all ethnic groups, the difference in this Gothenburg cohort is somewhat smaller but still prominent.[64]

There are surprisingly few randomized, placebo controlled trials investigating the efficacy of GH treatment in TS considering its widespread use for this indication.[62] Evaluating the height gain achieved with GH treatment is complicated, investigators have determined average height gains compared either to current placebo-treated controls [61,63] or to historical controls and baseline projected/predicted height.[66-69] According to the latest clinical practice guidelines for TS from 2017 a realistic expectation based on the available literature is a height gain of 5-8 cm, or about 1 cm per year.[41] In these guidelines, GH treatment is recommended, and with an as early start as possible (around 4–6 years of age) and preferably before 12–13 years since growth rate slows considerably at puberty.[67] GH is thus given as a daily subcutaneous injection at home (with the aid of a parent) for up to approximately 10 years and then discontinued after puberty.

Cognitive gains as a result of GH treatment in TS have not been seen, although there are only very few published studies evaluating this. Rovet and Holland reported in 1993 that the girls treated with GH in the Canadian placebo controlled trial reported improved self-perceived intellectual abilities.[61,70] A later study by Ross et al could not confirm these self-reported results, and GH treatment did not affect cognitive function or influence the non-verbal or neurocognitive impairments associated with TS when tested in early adolescence.[71]

OSTEOPOROSIS

Osteoporosis is a systemic skeletal disease characterized by low bone mass and deterioration of bone structure with a consequent increase in bone fragility. This leads to an increased risk for fractures, typically of the hip, spine, radius, and humerus.[72] Fracture of the hip is the most serious, leading to a 10-15% increase in mortality within one year after the fracture, and vertebral fractures cause significant pain and can cause long term disability.[73,74] Osteoporosis is 3.5 times more common in women than in men largely due to the loss of estrogen after menopause that leads to an accelerated bone loss in women.[75] It is estimated that around 21% of the women in Sweden over the age of 50 have osteoporosis and that their remaining lifetime probability of enduring any osteoporotic fracture could be as high as 46%.[76,77]

The prevalence of osteoporosis and fractures increases with age in both sexes and possible contributing factors to this are decreased physical activity and balance, muscle mass and body weight, low intake of calcium and protein, and hormonal aberrations, specifically, low levels of estrogen, vitamin D, and IGF-1.[78,79]

The diagnosis is confirmed if bone mineral density (BMD) is more than 2.5 standard deviations (SD) below the mean BMD value in a reference population of healthy young women (T-score).[80] However, pharmacological treatment is recommended even to those who have a history of spine or hip fracture or an elevated 10-year fracture risk of 15% or more using the Fracture Assessment Tool, FRAX® (http://www.shef.ac.uk/FRAX).[74,81] Treatment should also be considered for patients with an elevated fracture risk due to secondary osteoporosis, *e.g.* hyperparathyroidism, hyperthyroidism, chronic inflammatory disease, and treatment with corticosteroids.

Fall prevention and physical exercise are important non-pharmacologic steps that must be taken to prevent osteoporotic fractures, as well as counseling about cigarette smoking (which is linked to reduced BMD) and about excess alcohol intake (which can increase the risk of falls).[82] The pharmacologic agents that are currently approved for use in Sweden to treat osteoporosis are outlined in table 2.[83]

Table 2. Drugs currently recommended for treatment of osteoporosis and prevention of fractures

Anti-resorptive	**Anabolic**	**Supplies bone mineralization***
Bisphosophonates	Teriparatide	Calcium
Denosumab		Vitamin-D
Raloxifene		

*Administered in conjunction with bone-specific drugs.

Bone-specific drugs are generally classified as either anti-resorptive (targeting osteoclast-mediated bone resorption) or anabolic (stimulating osteoblasts to form new bone). The efficacy of calcium and vitamin-D supplementation as solitary treatments for osteoporosis and fracture prevention is controversial, so they are recommended for use in conjunction with bone-specific agents.

Hormonal factors are important in osteoporosis, and teriparatide – a parathyroid hormone (PTH) analogue – was approved for use to treat osteoporosis in 2004. PTH regulates the metabolism of calcium and phosphate in the skeleton and in the kidneys. It also acts directly on bone to increase bone resorption in order to mobilize calcium to the blood. However, on a longer timescale, PTH directly stimulates the formation of new bone via receptors on the osteoblasts and indirectly promotes bone growth by increasing the absorption of calcium in the small intestine and kidneys. The effect of a slightly elevated plasma PTH is usually anabolic to bone.[5] Teriparatide is currently the only anabolic drug on the market for osteoporosis. It is offered to patients with severe osteoporosis with either a history of fractures or an increased risk for fractures.

Growth Hormone Treatment in Postmenopausal Osteoporosis

GH and IGF-1 are also important regulators of bone remodeling, longitudinal bone growth, and osteoblastic function (Figure 3).[84,85] GH acts by increasing hepatic and skeletal IGF-1 production but also influences bone directly, independently of IGF-1.

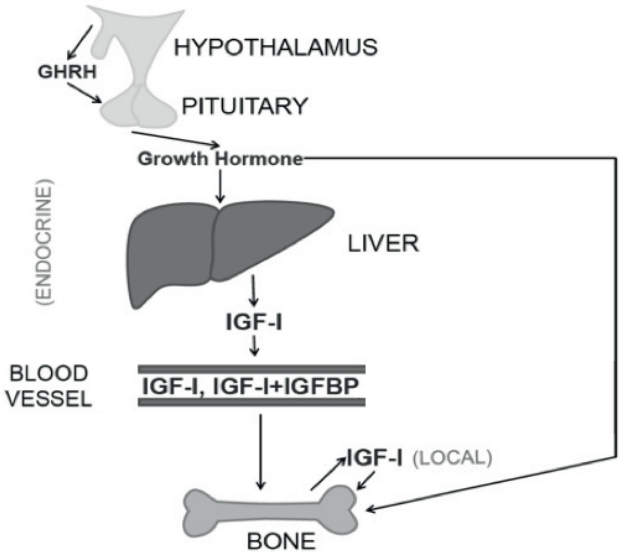

Figure 3. Overview of GH/IGF-1 regulation of skeletal growth, including both endocrine and local actions of IGF-1. Illustration courtesy of Dr. Subburaman Mohan and reproduced with permission from Elsevier.[85] *(IGFBP = Insulin-like Growth Factor Binding Protein)*

Several studies have indicated that postmenopausal osteoporosis is associated with lower levels of IGF-1.[79,86] GH treatment has been shown to have beneficial effects on bone in animal studies and in GH-deficient adults, a state that is also associated with an increased fracture incidence.[87,88] The first GH-treatment trial in osteoporosis was conducted in three male patients and published in 1975; osteoblast activity increased along with an increased bone turnover.[89] Since then, 10 GH treatment trials in postmenopausal osteoporosis have been published, and although there was a great deal of variation in dose, concomitant estrogen treatment, and treatment duration (from 1 week to 3 years), all but two studies reported a significant increase in bone formation, bone mineral content (BMC) and/or BMD.[90] The longest double-blind, placebo-controlled trial published to date, was conducted on 80 postmenopausal women with osteoporosis, for three years.[91] BMC increased by 14% in the group that received the highest GH dose and muscle mass increased concomitantly.

SUBJECTS AND METHODS

A quantitative approach was used when measuring HRQoL in relation to GH treatment and disease variables in women with TS and postmenopausal women with osteoporosis compared to a sample of women from the general population.

STUDY POPULATIONS

This thesis is based on studies done on two patient samples: one of women with Turner syndrome and one of women with postmenopausal osteoporosis, and two population-based cohorts.

Table 3. Overview of study designs, subjects and main outcomes. NHP = Nottingham Health Profile, PGWB=Psychological General Well-Being index, SF-36=Short-Form 36 and SRH=Self-rated Health 0-100. n.a.=not applicable

	Paper I	**Paper II**	**Paper III**	**Paper IV**
Design	Cross-sectional	Longitudinal 20 yrs	Longitudinal 10 yrs	Cross-sectional
Subjects	Turner syndrome	Turner syndrome	Post-menopausal osteoporosis	Population sample
No. of subjects	n=111	n=200	n=80	n=414
Age (yrs), mean±SD, min-max	30±4, (18-63)	28±11, (16-71 at baseline)	60±6, (50-70 at baseline)	63±9 (39-78)
Reference population*	Yes	Yes	Yes	n.a.
Main outcomes	HRQoL scores: NHP, PGWB	HRQoL scores: NHP, PGWB	HRQoL scores: SF-36. Fractures and bone data	HRQoL scores: NHP, PGWB, SF-36, SRH

*Details about reference populations can be found in Table 5.

Women with Turner syndrome

In papers I and II, women with suspected or diagnosed TS were recruited beginning in 1994 through an advertisement in the Turner patient magazine, by referral from the hospitals in the county of Västra Götaland with 1,5 million inhabitants, or transferred from the pediatric clinics in the county to the Turner Center at the Sahlgrenska University Hospital. The women with TS were monitored according to the Swedish and International clinical practice guidelines for TS and underwent clinical examination, testing, and HRQoL evaluation approximately every 5th year (Figure 4).[41,92-94] All of the patients were examined by the same internal medicine specialist/endocrinologist (Dr. Kerstin Landin-Wilhelmsen) and gynecologist (Dr. Inger Bryman) during the entire follow-up time.

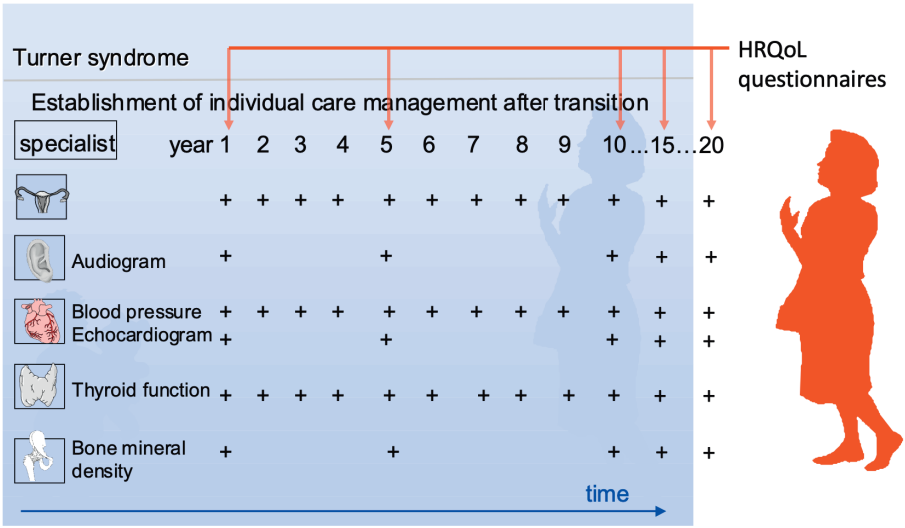

Figure 4. Schematic illustration of the examination program for TS according to the Swedish national guidelines.[94]

The inclusion criteria were: phenotypically female subjects, age ≥16 years, and a partial or complete absence of an X chromosome in at least 5% of leukocytes or buccal cells. There were no exclusion criteria. GH was given in childhood, 0.1 - 0.2 IU/kg/day, equivalent to 33 - 66 µg/kg/day, mainly in clinical trials.[67,95]

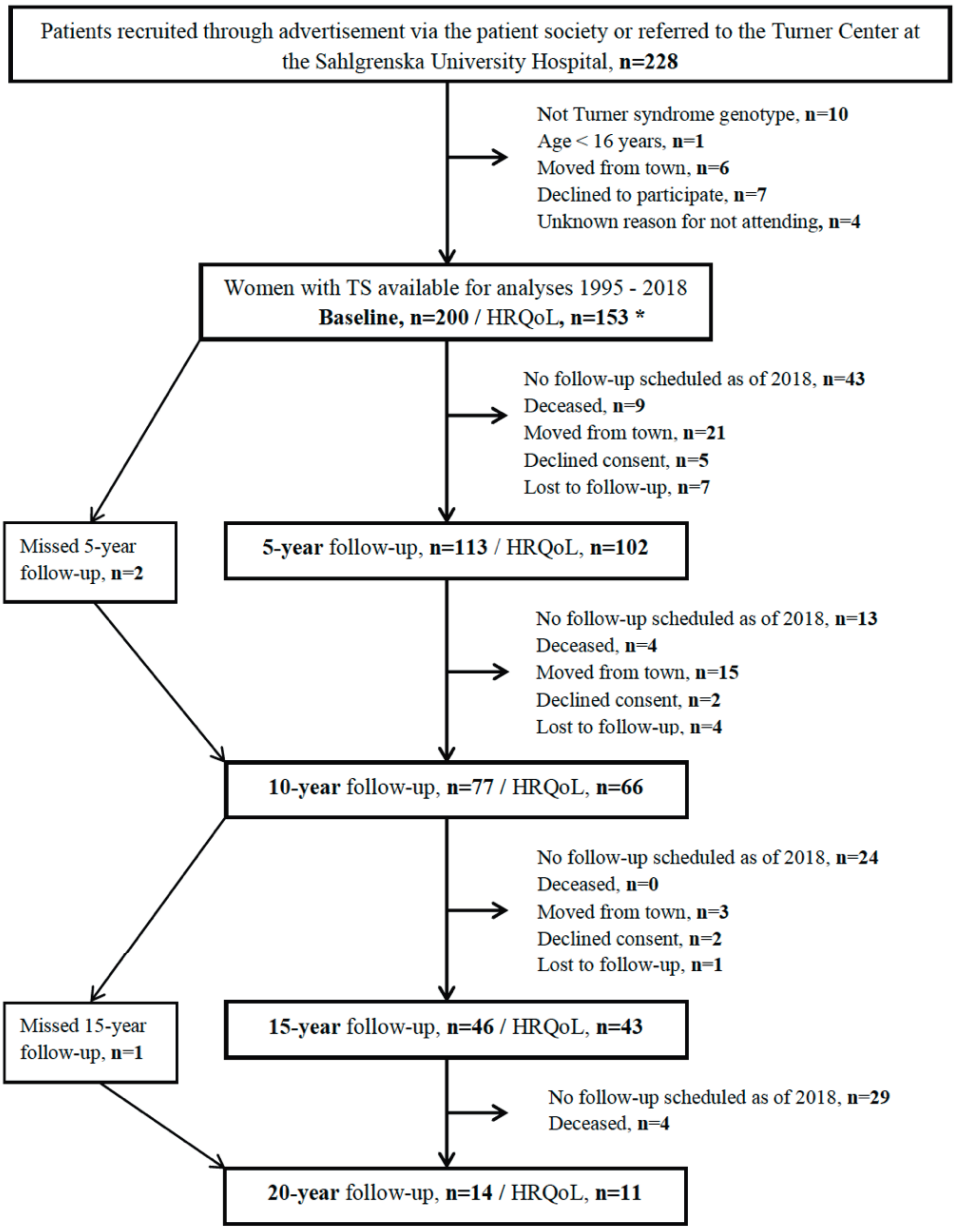

*Figure 5. Flow-chart of the 20-year follow-up of women with TS at the Turner Center, Sahlgrenska University Hospital. *178 women completed HRQoL questionnaires at least once. Reproduced from paper II with permission from Oxford University Press.*

In paper I the women who had completed questionnaires at baseline by 2007 were included in a cross-sectional study, n=111. In paper II, inclusion was continuous between 1995 and 2018, n=200, and re-evaluations were scheduled approximately every 5th year. Inclusion and follow-ups are illustrated in figure 5.

HRQoL questionnaires were completed at least once by 178 women, but not necessarily at baseline (89% participation rate in HRQoL measurement) (Table 4). The 22 women who did not complete any HRQoL questionnaires either actively declined consent (n=5), were not offered HRQoL questionnaires because they were under the age of 18 at baseline (n= 4), or were not offered HRQoL questionnaires because of an administrative error or did not turn in the questionnaires at the end of their visit (n=13).

Table 4. Frequency table of total number of HRQoL follow-ups that the 200 women with TS completed in paper II. Reproduced from paper II with permission from Oxford University Press.

Completed HRQoL measurements, (n)	**none**	**1**	**2**	**3**	**4**	**5**	**Total**
Women with TS, (n)	22	77	42	30	21	8	200

Women with Osteoporosis

Paper III is a follow-up study of bone and HRQoL measurements of 80 postmenopausal women with osteoporosis who had participated in a randomized, double-blind, placebo-controlled clinical trial with GH, either 1.0 IU/day or 2.5 IU/day subcutaneously for three years or corresponding volumes of placebo between 1995-1997.[91] Women with ongoing calcium/vitamin D and estrogen Hormone Replacement Therapy (HRT) were recruited during 1994–1995 from the Endocrine Outpatient Clinic, consultants in the city, and an advertisement in the local newspaper. Inclusion criteria were:

1. Osteoporosis according to the WHO criteria *i.e.*, Bone mineral density (BMD) equal to or lower than –2.5 SD of young adults (T-score) from the LUNAR USA reference population of the same gender measured at the lumbar spine using Dual energy X-ray Absorptiometry (DXA).[80]

2. HRT for at least 9 months.

Exclusion criteria were: diabetes, ischemic heart disease, heart failure, kidney disease, cancer, any other chronic disease or any disease affecting the skeleton, ongoing treatment with corticosteroids, and/or osteoclast inhibitors. A chest X-ray was performed before the start to exclude any subjects with heart enlargement or tumors.

Altogether, 451 women were screened for osteoporosis; 371 did not meet the inclusion criteria - the majority of whom did not have osteoporosis. Seventy-seven patients with osteoporosis according to the WHO's definition above were included. It was difficult to recruit 80 women fulfilling this criterion, so 3 patients with BMD T-score -2 SD and with at least one osteoporotic fracture were included. No subjects were lost in the 10 years of follow-up. In total, 7 subjects discontinued GH injections during the first 3 years. 6 subjects died (two of stroke, one of myocardial infarction, one of respiratory insufficiency, one of pulmonary cancer and one of kidney cancer) (Figure 6).

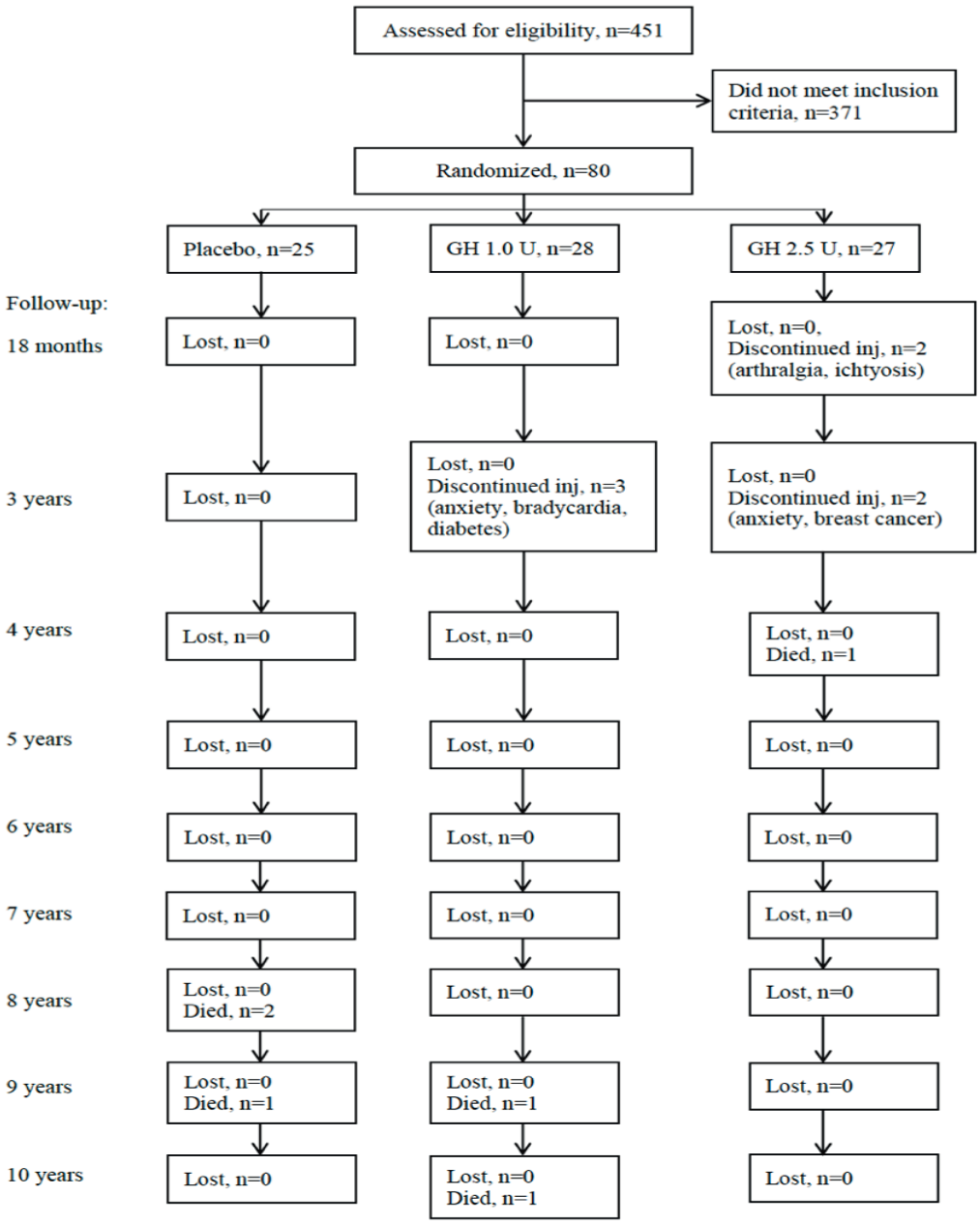

Figure 6. Flow-chart of enrollment and follow-up between 1995 and 2005 of women with postmenopausal osteoporosis. Population-based samples: WHO GOT MONICA Project

Population-based samples: WHO GOT MONICA Project

In papers I-IV, subjects from the The WHO MONItoring of trends and determinants in CArdiovascular disease – Gothenburg project (WHO MONICA) were used as subjects or reference subjects for HRQoL and medical and social factors. The WHO MONICA project monitored risk factors in three independent cross-sectional population surveys conducted every 5th year between 1985 and 1995.[96] One aim was to report levels of risk factors in the population to enable comparisons with studies in groups of people with disease.

In 1990, the second population screening was conducted in which 2,400 individuals (age 25-64, 50% women) were recruited from the Gothenburg city census, which is kept up to date within a maximum of 14 days. 2,312 individuals were eligible to sample (possible to contact) and 1,575 individuals participated (66% participation rate, 50% women). In the third screening in 1995, 2,612 individuals (age 25-64, 54% women) were recruited in a similar fashion, 2,563 individuals were eligible to sample and 1,618 individuals participated (62% participation rate, 54% women). All subjects were examined at the Section for Preventive Medicine, Department of Medicine, Sahlgrenska University Hospital.

A randomly selected subset of the subjects examined in 1995 (every 4th subject, and all of the women aged 45-64 years, in total n=662) underwent extra hormonal testing and they were invited for re-evaluation and assessment of HRQoL in 2008.[97] In total, 414 subjects completed re-examination in 2008 by two endocrinologists (Dr. Penelope Trimpou and Dr. Kerstin Landin-Wilhelmsen) (Figure 7, 62% participation rate, 77% women, age range 39-78 years).

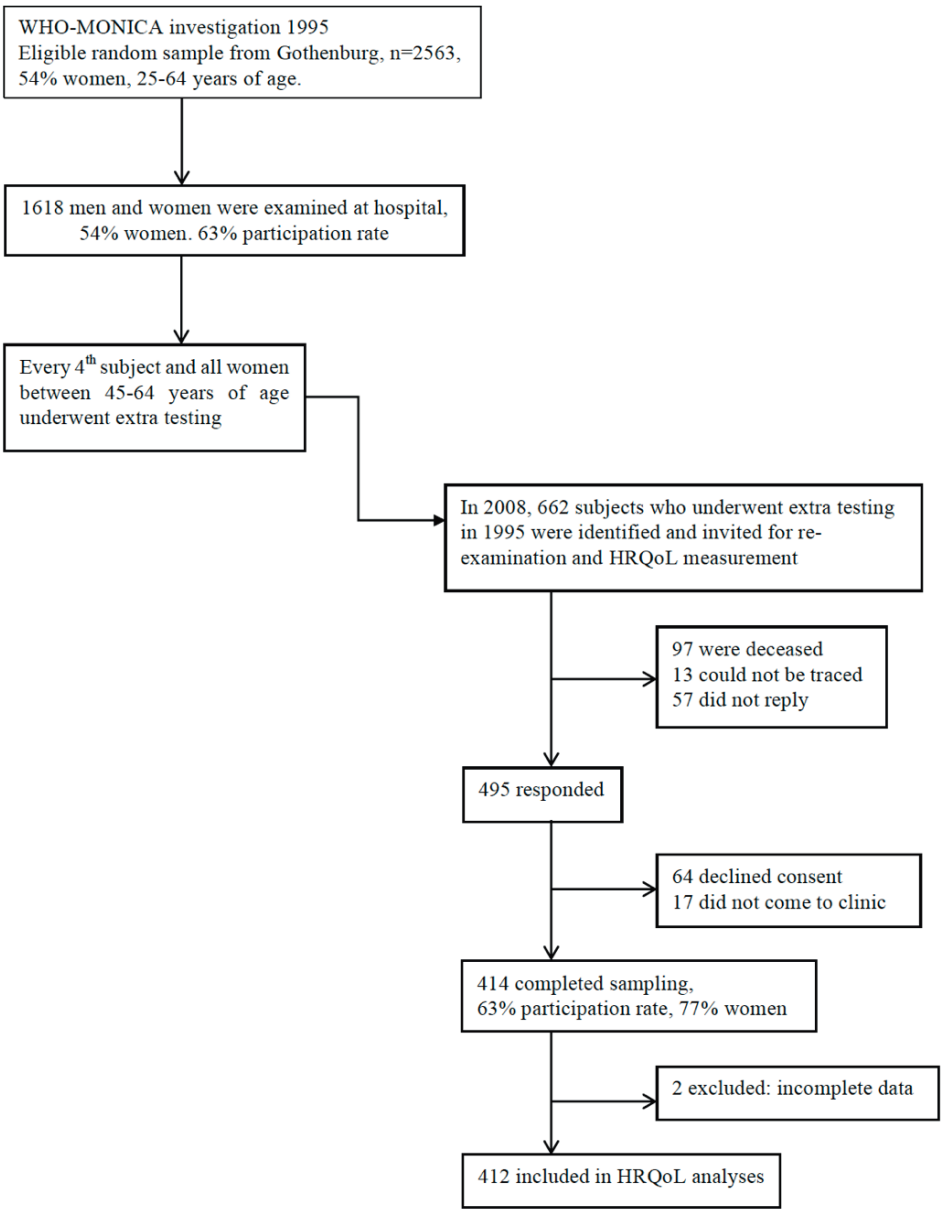

Figure 7. Flow chart of the subjects from WHO MONICA 1995 who underwent extra testing and who were re-examined in 2008.

A description of which subjects from the WHO MONICA investigations who were included in the studies in this thesis is presented in table 5.

Table 5. Overview of the use of the population-based samples in the papers in this thesis.

WHO MONICA investigations	**1990 cohort**	**1995 cohort**	**2008 re-examination of 1995 cohort**
Original study cohort	n=1,575, 50% women [96]	n=1,618, 54% women [96]	n=414, 77% women [97]
HRQoL measurement	Yes	No	Yes
Paper I	Reference population: age-matched with women with TS. n=111 mean age 32±6 yrs min-max 25-45 yrs		
Paper II		Reference population for women with TS at baseline n=400 women mean age 35±6 yrs min-max 25-45 yrs	Reference population for women with TS regarding HRQoL results. n=318 women mean age 64±9 yrs min-max 39-78 yrs
Paper III		Reference population for women with post-menopausal osteoporosis n=120 women mean age 60±6 yrs, min-max 55–64 yrs	Re-examination of same women from 1995 n=120 mean age 72±6 yrs min-max 67–76 yrs
Paper IV			All subjects n=414; n=318 women, n=96 men mean age 63± 9 yrs min-max 39-78 yrs

HRQOL INSTRUMENTS

In this thesis, four generic instruments were used to evaluate HRQoL.

Table 6. Overview of the HRQoL instruments used in this thesis.

HRQoL instrument	Nottingham Health Profile	Psychological General Well-Being Index	Short Form-36	Self-Rated Health scale
Paper I	✓	✓		
Paper II	✓	✓		
Paper III			✓	
Paper IV	✓	✓	✓	✓

The Nottingham Health Profile (NHP)

NHP measures aspects of subjective health using a two-part questionnaire.[33] In these studies the NHP part I was used. Part I is comprised of 38 statements covering six dimensions concerning distress or limitation of activity:

1. Emotional Reactions
2. Sleep
3. Energy
4. Pain
5. Physical Mobility
6. Social Isolation

The response format is yes or no, dimension scores range from 0 to 100 and each statement is weighted according to the level of severity. The higher the score, the greater the limitations/distress, *i.e.* the lower HRQoL. The NHP was developed in the 1980s but is still widely used, especially in Europe. It is useful because of its breadth and simplicity and is a suitable instrument for use in clinical practice and in populations where there are likely to be people with disabilities.[14]

The Psychological General Well-Being Index (PGWB)

The PGWB was designed to measure personal affective or emotional states reflecting a sense of well-being or distress intended for use in community surveys.[36] The PGWB includes 22 items, with a six-grade Likert style response format where a high score represents a better HRQoL. Sub-scales include:

1. Anxiety (range 5-30)
2. Depressed Mood (range 3-18)
3. Positive Well-being (range 4-24)
4. Self-control (range 3-18)
5. General Health (range 3-18)
6. Vitality (range 4-24)

The scores are also summarized into an overall well-being score: PGWB Total score (range 22-132). The PGWB has been used in clinical trials and has performed well in both population-based and mental health samples.[98]

Medical Outcomes Study Short Form-36 Questionnaire (SF-36)

The SF-36 is a multipurpose health survey comprised of 36 items where a high score represents a better HRQoL.[34] It yields an eight-scale profile of functional health and well-being (range for all sub-scales 0-100):

1. Physical Functioning
2. Role Physical
3. Bodily Pain
4. General Health
5. Vitality
6. Social Functioning
7. Role Emotional
8. Mental Health

It also generates psychometrically based physical and mental health summary measures: A Mental Component Summary and a Physical Component Summary (Figure 8). The summary scores are designed to have a population mean score of 50 with a standard deviation of 10 and

low scores indicate a greater impairment of QoL (range 0-100). The SF-36 has been proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments. [99]

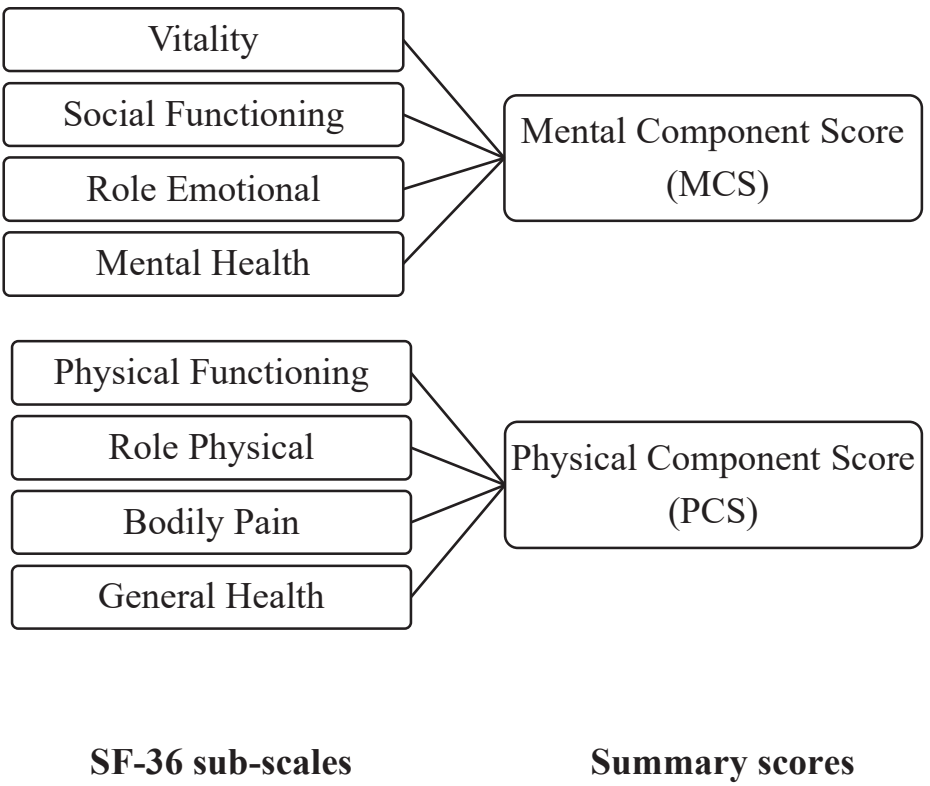

Figure 8. Composition of SF-36 summary scores.

Self-Rated Health (SRH) scale

SRH was measured with a single question. Subjects were asked to rate their current health status between 0 and 100 on a linear analogue self-assessment scale or "thermometer"; 0 being the worst conceivable level and 100 the best conceivable level. The item is identical to question number 6 published in the 1990 edition the EuroQol Research Foundation - 5 Dimension questionnaire™ (EQ-5D) (Figure 9).[35] Single-item health indicators have consistently been shown to be strong correlates of objective health and even as predictors of mortality.[29,100,101]

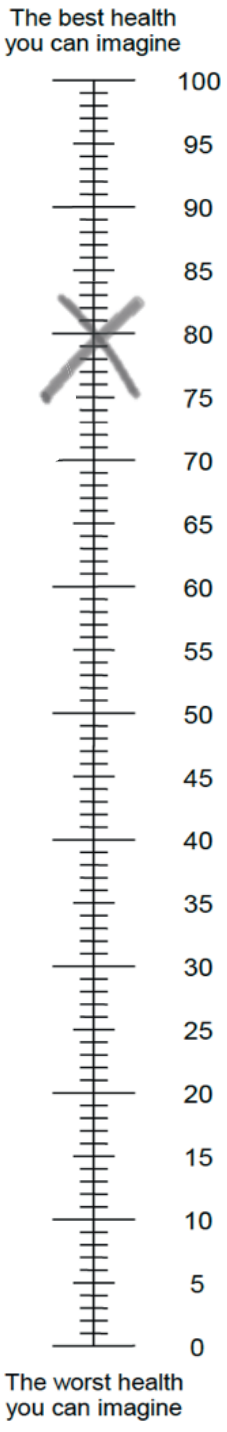

Figure 9. Visual analogue scale from EQ-5D™ - thermometer. © 1990 EuroQol Research Foundation. EQ-5D™ is a trade mark of the EuroQol Research Foundation. UK (English) v2.0. Reprinted with permission from EuroQol Research Foundation.

The X indicates the median score (80) for the population sample in paper IV.

Comparison between Instruments

To compare the results between the instruments in paper IV, 6 domains that were conceptually similar were identified: Social Functioning, Pain, Physical Functioning, Mental Health, Vitality, and General Health and the Summary Scores (Table 7). This categorization was made based on the content in the items themselves and supported by previously published studies using these instruments.[102-106] The questionnaires were administered in the same order to all subjects.

Table 7. Comparison of content of Nottingham Health Profile (NHP), Short-Form 36 (SF-36), Psychological General Well-being index (PGWB), and the Self-Rated Health (SRH) scale to identify domains that are conceptually similar. Reproduced from paper IV with permission from BMJ Publishing Group Ltd.

Domain name	NHP	SF-36	PGWB	SRH scale
Social Functioning	Social Isolation	Social Functioning	-	
Pain	Pain	Bodily Pain	-	
Physical Functioning	Physical Mobility	Physical Functioning	-	
Mental Health	Emotional Reactions	Mental Health	Anxiety & Depressed Mood	
Vitality	Energy	Vitality	Vitality	
General Health	-	General Health	General Health	Self-rated health
Summary Scores	-	Physical Component Summary & Mental Component Summary	PGWB Total-score	Self-rated health

SOMATIC AND SOCIAL VARIABLES

Anthropometry

Body weight was measured to the nearest 0.1 kg in the fasting state with all subjects in their underwear and barefoot. Body height was measured barefoot to the nearest 0.5 cm. Body mass index (BMI) was calculated as body weight divided by height squared (kilograms per square meter). Waist circumference was measured with a soft measuring tape midway between the lowest rib margin and the iliac crest in the standing position. Hip circumference was measured over the widest part of the gluteal region, and the waist to hip ratio was calculated. In the women with TS, the number of external TS stigmata was recorded at baseline by Drs. Landin-Wilhelmsen and Bryman.

Pharmacological treatments

Information on ongoing pharmacological treatment was asked for and coded according to the Anatomical Therapeutic Chemical (ATC) classification system for all subjects. In women with TS, GH and/or Oxandrolone therapy in childhood was recorded at baseline. Current treatment with HRT was recorded at baseline and at every follow-up.

Bone and cardiac measurements

BMD (g/cm^2), BMC (kg), body fat, and lean body mass, were measured with DXA (LUNAR DPX-L, Lunar radiation Inc, Madison, WI, USA) including total body, T-score at lumbar spine (anterior-posterior L_2-L_4), femoral neck and distal radius. Fractures of possible osteoporotic origin were recorded: distal radius, humerus, rib, vertebrae, femoral neck or trochanter, and ankle.

Blood pressure was measured to the nearest 2 mmHg. Echocardiography was performed on all women with TS according to international guidelines.[41] Cardiac left ventricular ejection fraction was estimated and the presence of cardiovascular malformation (bicuspid aortic valve and coarctation of the aorta) was recorded. If the echocardiography was deemed insufficient to determine the aortic valve structure, a magnetic resonance image examination of the heart was performed.

Biochemical analyses

Blood samples were drawn in fasting state and analyzed at the accredited Laboratory for Clinical Chemistry, Sahlgrenska University Hospital. The chromosome status in the TS women was based on both karyotyping and fluorescence in situ hybridization.[107]

Risk factors and social status

Social factors such as education level, civil status and children, employment status, physical activity in leisure time (sedentary, moderate, regular), use of tobacco, and use of hearing aid were asked for similarly in all subjects.

STATISTICAL METHODS

Descriptive statistics including mean, medians, and standard deviation values were calculated using conventional methods in all papers. Mantel-Haenszel's Chi-2 and Fisher's exact tests were used to compare differences between groups for discreet data. Group comparisons of continuous variables were made with Student's t-test.

In Paper I, multiple regression analyses and logistic regression models were used to test interactions between factors. In paper II analyses of variance were used to compare HRQoL outcomes since an adjustment for age was necessary. Due to limited amount of data, linear regression models were applied when analyzing the longitudinal data. In some of the analyses, it was possible to apply a random effects model (random intercept on individual level) but it was concluded that the results only changed marginally compared to the results from the ordinary linear regression. So, for the sake of simplicity when presenting the data, only ordinary linear regression results are shown and interpreted.

In paper IV, the percentage of subjects with lowest (floor effect) and highest (ceiling effect) possible scores were calculated. The non-parametric Mann-Whitney U test was used to compare results between groups, since the results were not normally distributed. Cohen's *d* test was used to calculate the standardized mean effect size between groups, $d > 0.25$ was considered educationally significant, $d > 0.5$ was considered clinically significant.[108] Internal consistency was examined using Cronbach's Alpha, $\alpha > 0.70$ was considered acceptable.

Correlation analyses between the instruments were focused on comparing the conceptually similar dimensions (Table 7) between the instruments used. Spearman's rho correlations (r_s) were used to analyze discriminant validity since the results were not normally distributed. Correlation coefficients were considered weak if $r_s < 0.30$, moderate if $r_s = 0.30 - 0.49$ and strong if $r_s \geq 0.50$. Regression analysis using the R^2 coefficient of determination was calculated for certain sub-scale comparisons. The presence of self-rated ill-health was defined using the SRH scale score split at the median. All scores below the median value were categorized as self-rated ill-health.

In papers I and III, $p<0.05$ (two-sided test) was considered statistically significant. In papers II and IV, $p < 0.01$ (two-sided test) was considered statistically significant to reduce the risk of Type I error. In paper II, 99% Confidence Intervals (99% CI) were calculated.

All statistical analyses were calculated using Statistical Package for the Social Sciences (SPSS v. 24) software or Microsoft Excel. SF-36 scores were calculated using scoring software obtained from the HRQL-group at Gothenburg University for paper III and from Optum™ (license number QM03712) in paper IV. Mental and Physical component scores were calculated using 1998 Swedish norms[109] in paper III and using 1998 US norms in paper IV.

ETHICAL CONSIDERATIONS

Ensuring personal integrity is imperative when conducting epidemiological studies such as these. All data was collected and handled by authorized personnel only. Every patient/subject in these studies was assigned a unique anonymous identification code making personal information and data impossible to trace back to the individual. Analyses and presentation of results were only performed on a group level with no possibility to identify unique individuals. All subjects gave their written and informed consent prior to participation in all of the studies. Subjects could withdraw their consent at any time and were thereafter excluded.

All studies were approved by the Regional Ethical Review Board in Gothenburg:

- Turner syndrome monitoring program: 1995 Dnr. 456-94 and 2002 Dnr. 242-02.
- Growth hormone trial and follow-up in postmenopausal osteoporosis: 1993 Dnr. 386-92 and 2000 Dnr. 543-00
- WHO GOT MONICA Project: 1994 Dnr. 076-05, 2006 Dnr. 088-06, and 2011 Dnr. T282-11.

We are also aware that repeatedly asking very personal questions related to HRQoL – albeit in a questionnaire format – may have been construed as prying from the participants' perspective. The women with TS and the women with osteoporosis were repeatedly asked to complete the questionnaires, so information was also repeatedly given reminding them of the voluntary nature of their participation in the HRQoL evaluation especially. Careful consideration was given to the choice of HRQoL instruments in each group to ensure the relevancy of the questions as much as possible.

Since much of the research on GH treatment in non-GH deficient patients has been initiated and sponsored by the pharmaceutical industry it is pertinent to evaluate the treatment independently and with longitudinal studies. All of the studies in this thesis are investigator initiated, performed in an academic setting at the Sahlgrenska University hospital, and were sponsored by grants from non-profit organizations.

It must, however, be acknowledged that the incentive to monitor girls and women with TS may not have been as strong without the introduction of recombinant GH to treat short stature the 1980's. What we now consider optimal and modern treatment of TS all followed in the wake of the introduction of GH treatment: earlier diagnosis, age-appropriate puberty induction and estrogen replacement therapy, regular monitoring at specialist health care units in both child- and adulthood, interest in the psychosocial implications of the syndrome, and the introduction of international clinical guidelines.[41,92,93,110] All of which have benefitted the TS patient group as a whole.

MAIN RESULTS AND COMMENTS

GROWTH HORMONE TREATMENT AND HRQOL IN TURNER SYNDROME (I & II)

Of the 200 women with TS, 63% had received GH treatment during childhood. Continuous HRT was used at some time during the follow-up by 85%. The remaining 15% had spontaneous puberty or did not wish to use HRT. A treatment profile for the whole group is illustrated in figure 10 and is accounted for in detail in paper II, table 1.

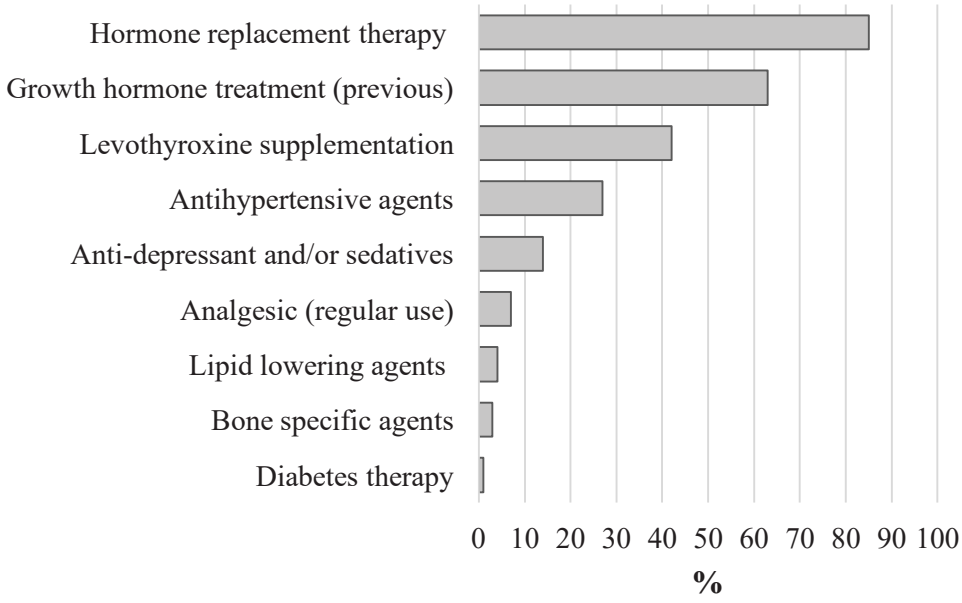

Figure 10. Average treatment prevalence (%) in the 200 women with TS during the 20 years of monitoring at the Turner Center, Sahlgrenska University hospital.

The women who had never received GH treatment were on average older when they were diagnosed than the women who had received GH treatment (Figure 11). A more detailed comparison between the groups at baseline and at every follow-up the can be seen in paper II, Table 2.

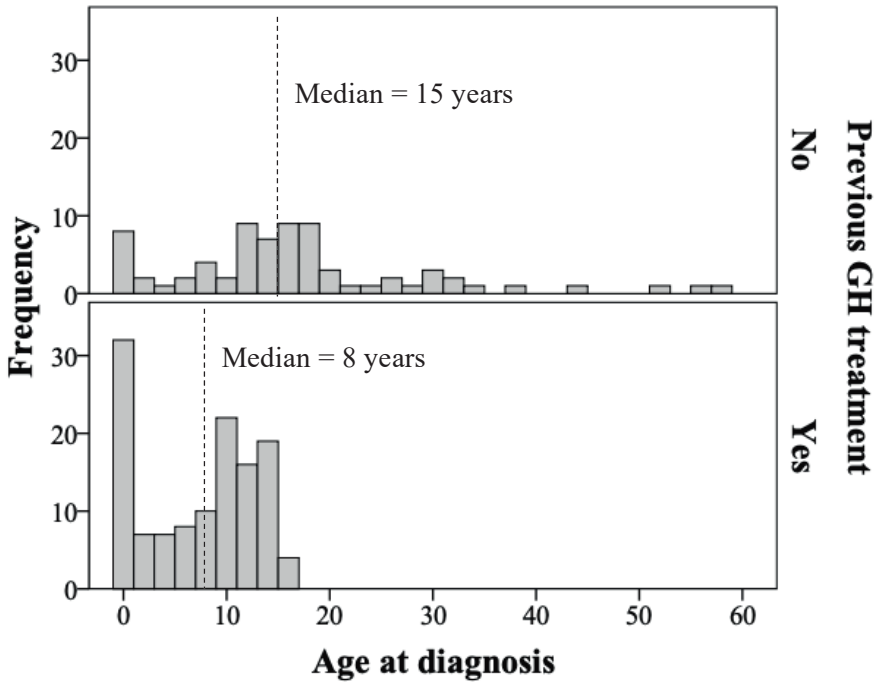

Figure 11. Frequency diagrams of age at TS diagnosis. Dotted line denotes median age at diagnosis within the groups. p<0.01 (unadjusted) between untreated (upper) and GH treated (lower) women with TS.

Main results paper I: In the cross-sectional analysis of adult women with TS, no significant impact on HRQoL attributable to GH treatment could be found, despite the mean 5.1 cm taller adult height, except for less pain in the NHP. Compared to an age-matched sample of women in the population, the TS women reported more problems with Social isolation (Figure 12).

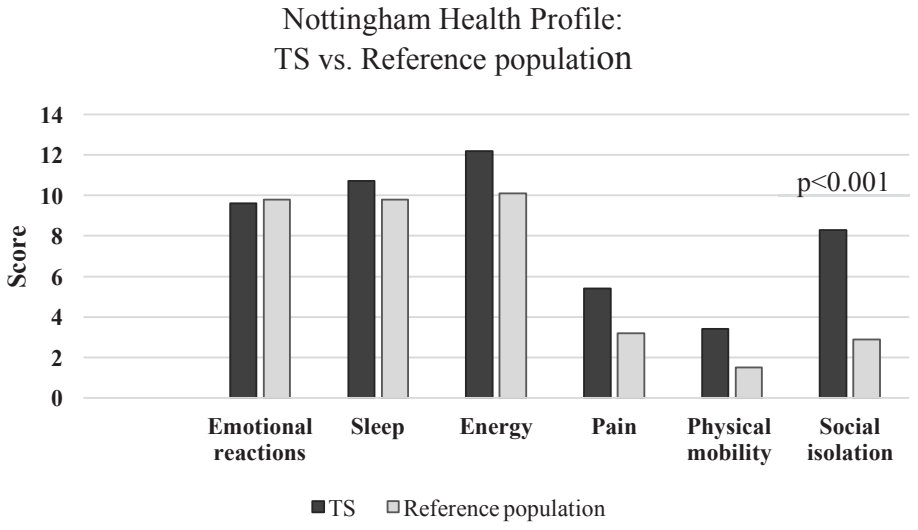

Figure 12. NHP scales in the whole TS cohort (n = 111) and the age-matched, randomly selected reference population (n = 111). p < 0.001 between TS and the reference population in the social isolation domain. Higher score = worse HRQoL. Reproduced from paper I with permission from Oxford University Press.

Main results paper II: No association between previous GH treatment and HRQoL was found during the up to 20-yrs of follow-up in women with TS after adjustment for age, despite the mean 5.7 cm taller adult height (Table 8). HRQoL was only associated with adult height in one of the 13 subscales used (NHP Emotional reactions) after adjustment for age ($p<0.01$). HRQoL was negatively affected by higher age, higher age at diagnosis, and hearing impairment. The HRQoL of the women with TS and the reference population was similar.

Table 8. HRQoL in TS women, Growth hormone treated (GH+) and not Growth hormone treated (GH-) shown separately. Psychological General Well-being index (PGWB) and the Nottingham Health Profile (NHP).

	TS Baseline		**TS 5-year follow-up**		**TS 10-year follow-up**		**TS 15-year follow-up**		**TS 20-year follow-up**	
	GH - n=55	**GH + n=98**	**GH - n=49**	**GH + n=53**	**GH - n=36**	**GH + n=30**	**GH - n=28**	**GH + n=15**	**GH - n=6**	**GH + n=5**
Age (yr) mean (SD); min-max	39 (12); 19-66 *	21 (3); 18-35	44 (10); 30-62 *	28 (3); 23-39	60 (9); 38-67 *	32 (3); 27-37	56 (10); 43-73 *	38 (2); 34-42	60 (10); 49-78 *	44 (2); 40-47
Height (cm), mean (SD); min-max	150 (7); 135-165*	156 (6); 131-168	149 (6); 135-161*	155 (6) 132-164	150 (6); 137-162*	154 (5); 141-164	150 (7); 138-161	153 (6); 141-162	150 (8); 140-162	150 (5); 141-157
PGWB, mean score (SD)										
Anxiety	23 (4)	22 (5)	22 (4)	23 (5)	23 (4)	25 (4)	23 (3)	24 (4)	21 (4)	24 (2)
Depressed mood	16 (2)	15 (3)	15 (3)	16 (2)	15 (3)	17 (2)	15 (2)	15 (2)	15 (2)	17 (2)
Positive well-being	17 (3)	17 (3)	16 (3)	17 (3)	16 (3)	18 (3)	16 (3)	17 (4)	15 (2)	17 (2)
Self-control	15 (2)	15 (3)	14 (2)	15 (3)	15 (2)	16 (2)	14 (2)	15 (3)	15 (2)	16 (1)
General health	15 (3)	16 (2)	15 (3)	16 (2)	14 (3)	16 (2)	14 (3)	15 (3)	12 (2)	15 (2)
Vitality	17 (3)	17 (4)	15 (4)	18 (4)	16 (3)	18 (3)	17 (4)	17 (3)	15 (1)	19 (2)
Total Score	101 (15)	103 (19)	97 (16)	104 (17)	98 (17)	109 (12)	99 (13)	104 (16)	95 (10)	108 (8)
NHP, mean score (SD)										
Energy	11 (23)	15 (29)	17 (27)	10 (23)	12 (27)	10 (25)	11 (26)	14 (26)	17 (28)	0 (0)
Emotional Reaction	9 (16)	13 (22)	18 (29)	10 (18)	10 (19)	5 (10)	9 (20)	9 (18)	3 (4)	0 (0)
Sleep	13 (23)	12 (21)	22 (29)	10 (18)	14 (20)	6 (13)	17 (24)	13 (28)	29 (35)	9 (14)
Pain	12 (24)	1 (9)	12 (26)	4 (15)	8 (18)	1 (2)	14 (25)	4 (12)	27 (34)	0 (0)
Physical Mobility	4 (10)	2 (7)	8 (16)	2 (4)	8 (14)	1 (5)	9 (14)	5 (13)	24 (34)	7 (16)
Social Isolation	9 (20)	12 (23)	11 (23)	10 (21)	7 (18)	3 (8)	13 (23)	10 (19)	17 (22)	10 (13)

*$p<0.01$ (un-adjusted) between GH treated and untreated TS women at baseline and every follow-up (Student's T-test)

Comments on papers I & II

HRQoL in Adult Women with Turner Syndrome

There is no TS specific HRQoL instrument. This means that all of the conclusions that have been drawn so far on the HRQoL of women with TS are based on results from generic instruments. The benefit of this is that comparisons with reference populations can be made, and are often made in the literature, but we may be missing critical TS-specific factors that affect their HRQoL that the generic questionnaires are insensitive to. The NHP and PGWB were carefully chosen to reflect the breadth of issues commonly reported by women with TS during psychological evaluations and semi-structured interviews.[111] The two instruments complement one another; the NHP deliberately focuses on health problems while the PGWB includes aspects of positive well-being. Both instruments have also shown adequate case-detection ability and/or treatment sensitivity in other patient groups.[112-116]

There are very few studies that report HRQoL outcome measures in women with TS later in adulthood (> 25 years of age). It is important to consider the psychological and somatic consequences of TS in a life-span perspective since the features of the disorder may differ in expression and importance throughout life.[110,117]

Psychological, social and sexual problems in girls and women with TS are often reported but vary considerably and far from all women with TS have these problems.[118,119,111,120] Several cross-sectional studies have shown that older adults with TS (mean age > 30) reported more problems with social anxiety and social isolation compared to healthy controls.[111,121](I) Lower self-esteem and HRQoL have been shown to be associated with late puberty and absence of sexual activity, which underlines the importance of age appropriate puberty induction.[117,122] Otological involvement and hearing loss also seem to be associated with lower self-esteem and lower HRQoL.[122,123](II)

One longitudinal study of HRQoL in women with TS living in Norway showed that the women with TS reported a lower life satisfaction and lower self-reported general health at follow-up compared to the reference population.[55] However this was not the case in paper II.

No association has been seen between HRQoL and karyotype,[124](I,II) burden of stigmata,[117,125](I,II) or other factors related specifically to TS such as hypothyroidism and body composition.(II) This is surprising, and may be a result of the close and proactive treatment these women receive. However, the results regarding the association between HRQoL and the presence of cardiovascular malformations are contradictory. The presence of any cardiovascular malformation was associated with lower scores in the physical functioning domain and general health in a French cohort of young women with TS,[123] while it was *not* associated with HRQoL in the studies I and II. This may be because this cohort is older on average and they may have adapted to their condition, or because they participate in a regular monitoring program at a specialist clinic.

HRQoL in the physical functioning and pain domains seems to be compromised in TS in comparison to reference populations.[55,124](I) One study showed that the women with TS had more problems with mobility the older they were in comparison with controls which would explain the higher proportion that is on sick leave and have retired early (before the age of 65).[52] A possible explanation for this strain on physical functioning could be short stature or smaller body constitution in general, even if height *per se* has not consistently been shown to be associated with HRQoL.[123,126](I,II)

Growth Hormone Treatment of Children to Increase Height

The main objective of treating children with short stature with GH, regardless of etiology, is taller stature, with the assumption that being short reduces QoL in childhood as well as in adulthood.[127-129] This commonly held belief, in combination with the advent of readily available recombinant GH in the 1980s, its efficacy, and the fact that it is well tolerated has bolstered the rationale for treating growth deficient children without GH deficiency.[130,131] Children with TS, Prader-Willi syndrome, chronic renal insufficiency, children that are born small for gestational age without growth catch-up, and even otherwise seemingly healthy children with idiopathic short stature (in North America) are offered GH at a very young age even though they are not strictly GH-deficient.

After the US Food and Drug Administration approved the use of GH in children of with idiopathic short stature in 2003,[132] debate ensued as to

which patients should be treated and what the goals and costs of increasing height should be.[133-136] Even if this controversy has been mainly concentrated on the relevance of GH treatment in idiopathic short stature, it should prompt us to reflect upon which bases we have for treating the children without GH deficiency, now that we have over 30 years of clinical perspective and research to reflect upon.

There is, so far, no evidence supporting an elevated long-term post-treatment mortality attributable to GH treatment in Sweden.[137] A French study reported in 2010 that GH treatment was associated with an increased standardized mortality ratio in young adults with isolated GH deficiency, idiopathic short stature, or who were born small for gestational age, as well as an increased mortality rate specifically due to bone tumors and to cerebrovascular diseases.[138] However, the latter results were not repeated in a similar cohort of patients from Sweden, the Netherlands, and Belgium.[139] The increased standardized mortality ratio was, however, confirmed in a Swedish study of the same group of patients, but they concluded that this was due to different birth characteristics in the GH treated patients compared to the entire Swedish population born 1973-2010.[137] In the TS cohort of the present study, the risk for aortic dissection was not elevated in the women who had previously received GH compared to the GH naïve women.[140]

HRQoL and psychosocial outcomes in adults who received GH treatment as children are important when evaluating the success and efficiency of GH treatment.[135] It is therefore relevant to know whether height is a factor that affects HRQoL in general. There are, to my knowledge, only two published studies that address the association of HRQoL and height specifically in adults in the general population, one based in the United Kingdom using the EQ-5D,[141] and the other in France using the SF-36.[142] Both have flaws: they are both cross-sectional and can therefore not draw conclusions on causality and the former is industry sponsored which may affect the conclusions the authors made. Furthermore, the results are contradictory, but both conclude that the very shortest subjects (height < - 2 height standard deviation scores in the British study and < - 4 height standard deviation scores in the French study) were more likely to report problems with physical functioning than those of normal height. It is interesting to note that neither study showed clinically significant associations between

height and HRQoL domains concerning mental health and/or social functioning. In paper II, no statistically significant associations were found after age-adjustment between any of the HRQoL domains measured and height in the reference population of women from the population.

Being taller is associated with favorable early environment, nutrition, medical condition, income and education in both men and women.[143-145] But whether height is in fact a factor that is important for psychosocial functioning and HRQoL in childhood or adulthood is not entirely clear and evidence in favor of this theory is scant.[146] Studies of children and adults of short stature without GH-deficiency have not predictably shown that stature is associated with HRQoL or psychosocial functioning.[133,147,148] And most studies evaluating psychological outcomes of GH treatment have a high risk of bias which undermines the results.[136] We must also assume that most of the children being treated with GH are aware of the indication, causing an implicit projection of societal ideals and norms about being short onto them. It is therefore not unthinkable that this causes a bias that affects how they answer when we ask them about how their height impacts them when they are adults.

HRQoL in relation to previous Growth Hormone Treatment in Turner Syndrome

Studies systematically evaluating the effects of GH treatment to promote growth on QoL are very scarce and no randomized placebo-controlled trials of GH treatment in TS with long follow-ups have been published with HRQoL outcomes.[135]

No benefit or adverse effect of GH treatment could be found in HRQoL of the young women (mean age 20 years) with TS who had participated in the only randomized, placebo-controlled trial of GH treatment which has been published that reported HRQoL outcomes.[126] However, the sample size was small (n=34) and may not have had the statistical power to exclude a clinically relevant benefit of GH on HRQoL. Most other studies that draw conclusions on GH treatment's influence on HRQoL in TS are either very small,[124] or do so in comparison with women in the population, and do not compare the GH treated women to the untreated women.[123,149-151] In paper I the GH treated women reported less pain

than the untreated women after age adjustment.(I) In the longitudinal follow-up, there was no significant association between HRQoL and a past history of GH treatment at baseline or during follow-up.(II) In an American study of 240 women with TS (mean age approx. 30 years) a past history of GH treatment was not related to level of education, employment status, or marriage rate either.[54] Similarly, a French register study showed that GH treated women with TS had similar HRQoL and social status compared to a reference population and that height was not associated with psychosocial or HRQoL outcomes.[123]

We know from clinical experience and from the literature that height and height-gain after GH treatment is a main concern for TS patients and their parents, especially when they are young.[111] However, evidence linking a higher HRQoL later in life to taller adult height and/or GH treatment is scant and contradictory. An association between HRQoL and height, or height increase, after GH treatment in TS was not drawn in several studies,[123,126,152,153](I,II) while three other studies have reported that height was positively correlated with the physical functioning domains of HRQoL.[52,124,149] None of the latter were placebo controlled trails or longitudinal in their design. Another cross-sectional study of a cohort of women with TS in Poland, reported that life satisfaction was negatively associated with a dissatisfaction with short stature specifically, while height *per se* was not.[154]

Medical follow-up in adulthood is very important, so everything must be done to ensure that the transition from pediatric to adult care goes smoothly.[155] It would be a shame if the daily GH injections in childhood contribute to a "health-care fatigue" that may cause the young women on the verge of transition to adult care to choose not to participate in a monitoring program as adults. This may leave them unnecessarily vulnerable to premature illness.[156]

GH treatment is cumbersome and expensive, and the height-gain is relatively small. The main objective of GH treatment in girls with TS is to increase their height in the hope that it increases their HRQoL not only in childhood but also in adulthood and eases physical strains on the body that a smaller body constitution may entail. The results presented here (papers I and II) do not support our hypothesis that GH treatment and taller stature increase HRQoL in adulthood. The lack of convincing evidence linking adult height to a better HRQoL (cited above), must

prompt us to question whether recommending GH treatment for short stature to all girls with TS is justified.

Limitations, papers I &II

The paradigm shift in the way women with TS are treated and monitored after the introduction of GH to treat short stature in TS created a cohort effect, or generational difference, within TS. This resulted in, not only an age difference between the GH treated and untreated TS women, but also in a difference in age at diagnosis, a difference in when and how puberty was induced, and in how they were monitored during childhood, adolescence and in adulthood. It is also worth noting that the group characterized as being "treated with GH" in these studies is heterogeneous regarding duration of GH treatment, the daily GH dose, the addition of oxandrolone treatment, and mode and timing of puberty induction; all of which may have had an effect on adult height and on HRQoL.

According to the prevalence of TS (1/2,500), only about half of the women with TS in the population have been diagnosed – meaning that we have only studied the women with TS who (we presume) have the most severe somatic, psychological or social problems related to the syndrome that have led to diagnosis. This may have led us to overestimate the problems that women with TS in general face. However, the karyotype distribution of the women in this study was similar to that of other clinical Turner registers, so the results should be applicable to other clinical cohorts of women with the diagnosis.[49,157]

The results may have been skewed by the patients who were lost to follow-up, who died during the follow-up time and who did not complete HRQoL questionnaires at their follow-up visits. The generic HRQoL questionnaires used here may be insensitive to factors that affect women with TS specifically, like height, potentially causing us to underestimate the scope of problems in the group even if the instruments were chosen carefully to reflect a wide range of problems that women with TS face. The comparison between the women with TS and the women in the population may have been affected by the age-range disparity at baseline.

GROWTH HORMONE TREATMENT AND HRQOL IN OSTEOPOROSIS (III)

Main results paper III: BMD and BMC increased in a dose-dependent way in the GH-treated groups at year 4.[91] At 10 years, both BMD and BMC had decreased to levels that were similar to before treatment start. The fracture incidence (albeit similar between the treatment and placebo groups) decreased from 56% before inclusion to 28% during the 10 years they were followed-up. Fracture incidence increased in the sample from the general population of similar age during follow-up (Figure 13).

The GH treatment was well tolerated and no increased mortality was attributable to the treatment. At 10 years, 41% had stopped HRT, 23% had started treatment with bisphosphonates due to fractures, and 3% had received teriparatide due to established osteoporosis and side effects from bisphosphonates. In the reference population, use of HRT had decreased from 40% to 8%, and the use of bone-specific agents was 4% at follow-up. GH treatment was not associated with a change in HRQoL in women with postmenopausal osteoporosis. HRQoL was similar to women in the general population.

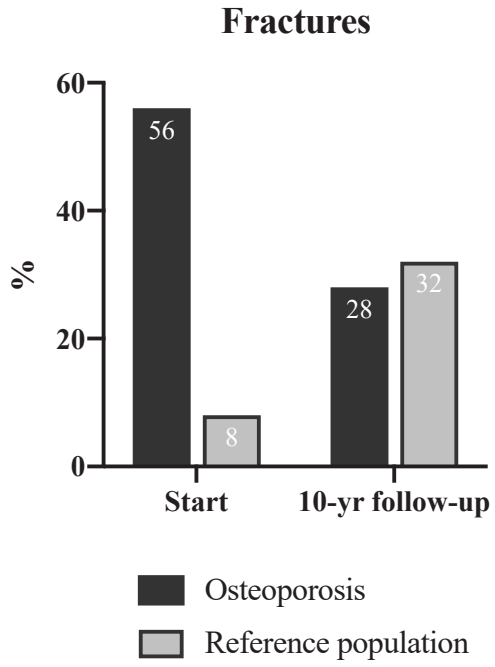

Figure 13. The number of fractures (%) in osteoporotic women and controls at start of GH treatment and at the 10-year follow-up. $p<0.001$ between patients and controls at start. $p<0.001$ within both groups at start and at follow-up. There was no significant difference between the patients and controls at follow-up. (III)

Comments on paper III

HRQoL in Osteoporosis

There are several osteoporosis specific HRQoL instruments available today; the two most commonly used are the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO-41)[158] which is self-administered and comprised of 41 questions and the Osteoporosis Quality of Life Questionnaire (OQLQ)[159] which is administered via interview and comprised of 30 questions.[160] Both were developed for women with vertebral fracture and as instruments to evaluate HRQoL in clinical trials. Since the QUALEFFO-41 is self-administered and less resource-intensive than the OQLQ, it has become the most widespread osteoporosis specific HRQoL instrument in the literature. It has been translated to Swedish but no validation studies of the Swedish version were found at the time of writing this thesis. Generic questionnaires are very commonly used to evaluate HRQoL in osteoporosis, most notably the SF-36, the NHP, the Sickness Impact Profile, and the EQ-5D.[32] The SF-36, used here, includes domains like pain, physical functioning, role physical and general health - all aspects of HRQoL that one would expect should be affected by osteoporosis which in turn affects the musculoskeletal system. Furthermore, the SF-36 has shown discriminative ability for the presence of disability/ chronic disease/handicap in all of its subscales.[109,161]

HRQoL is most obviously affected by the fractures associated with osteoporosis, both in the short and longer term and research has been mainly concentrated on this connection.[32,162] The loss in HRQoL is most severe after hip fracture but is also affected in patients with the other osteoporosis associated fractures mentioned earlier. Furthermore, HRQoL does not seem to be completely restored after a hip fracture (in the patients that survive) compared to before the fracture or in comparison with reference populations.[163-165] It has been suggested that osteoporosis *per se* - even without fracture - may be associated with lower HRQoL particularly with regards to pain, physical functioning, physical and mental perception, general health and vitality compared to controls.[166-169]

HRQoL in relation to Growth Hormone Treatment in Osteoporosis

Little is known about HRQoL in relation to anabolic treatment in patients with osteoporosis and the number of studies measuring it are very limited. Teriparatide has been shown to be beneficial for HRQoL in a longitudinal, uncontrolled, industry driven study over 3.5 years in subjects with severe osteoporosis using the EQ-5D.[170] Progressive improvements were observed from baseline in all five domains of the EQ-5D, the largest improvements occurred in the domains of pain and discomfort and usual activities. However, another study spanning a year and a half, showed no difference in HRQoL using the SF-36, and a visual analogue scale evaluating hip pain in patients treated with teriparatide compared to risendronate (a bisphosphonate).[171] In the case of GH treatment, the only known study to examine HRQoL outcomes in relation to GH treatment is paper III. No statistically significant change was found in any of the HRQoL domains measured between the GH treatment/placebo groups in postmenopausal osteoporosis, despite beneficial bone outcomes after 10-years of follow-up or any difference in comparison with a reference population of age-matched women using the SF-36. These results do not support the hypothesis that GH treatment increases HRQoL of women with postmenopausal osteoporosis.

Limitations, paper III

It is perhaps not surprising that GH treatment in the women with postmenopausal osteoporosis was not associated with improved HRQoL since the fracture incidence was evenly distributed between the treatment groups and the placebo group. It is fractures that are primarily associated with a decrease in HRQoL.[32,160] Alternatively, the lack of difference in HRQoL may mirror the small group size, a group size of approximately 25 can detect only relatively large differences in changes over time (approx. 20-point difference) between experimental groups with a repeated measures study design.[109] Even if GH treatment had a positive effect on bone variables and muscle mass, the fracture reduction seen in the patient groups is likely due to the regular clinical care, advice, and other bone-specific treatment(s) rather than on the GH treatment alone since there was no difference in fracture incidence between the treatment groups and the placebo group.

The reference group from the general population was not part of the original GH clinical trial.[91] It was considered relevant to include a comparative sample from the population during follow-up considering the under-diagnosis and under-treatment of osteoporosis that is still a major concern as the population ages and the prevalence of osteoporotic fractures increases.[172] The reference sample clearly reflects the underuse of the newly developed bone-specific drugs in general, and of especially anabolic agents.

HRQOL INSTRUMENT VALIDITY (IV)

Paper IV: In a population sample of men and women (of whom the women were used as a reference population in papers I-III), all of the eight SF-36 subscales and four of the six subscales in the PGWB had Cronbach α-coefficients >0.80 indicating high internal consistency. The NHP yielded generally lower internal consistency estimates than the other two (range α = 0.66–0.87) but only two subscales (social isolation and sleep) fell below the standard recommended α>0.70 for group comparisons.

There was a high concordance between the different instruments for evaluating HRQoL within each domain that was conceptually similar, except in the Social functioning domain. Furthermore, the SRH scale score correlated significantly with all the other instruments' sub-scales.

The average number of school years was 12 and >90% had been employed but were retired at the time of this investigation. The number of medications taken daily was considered a proxy for burden of disease. Men and women scored similarly in all the instruments' sub-scales and in the SRH after adjustment for the number of medications taken daily (Table 9).

Table 9. Disease burden characterized as number of medications taken daily in the whole group and in men and women respectively.

	Number of medications taken daily			
	0	1-2	3-5	6-10
All, n (%)	144 (35%)	130 (32%)	100 (24%)	38 (9%)
Male, n (%)	46 (48%)	33 (34%)	10 (11%)	6 (6%)
Female, n (%)	98 (31%)	97 (31%)	90 (28%)	32 (10%)

p<0.001, mean number of daily medications men vs. women (Students t-test).

The NHP, the PGWB, and the SF-36 discriminated the presence of self-rated ill or good health using the SRH split at the median score = 80. In addition, there was a strong negative association between HRQoL and the number of current regular daily medications taken in all of the instrument's subscales (p<0.01 for all) (Figures 14-17).

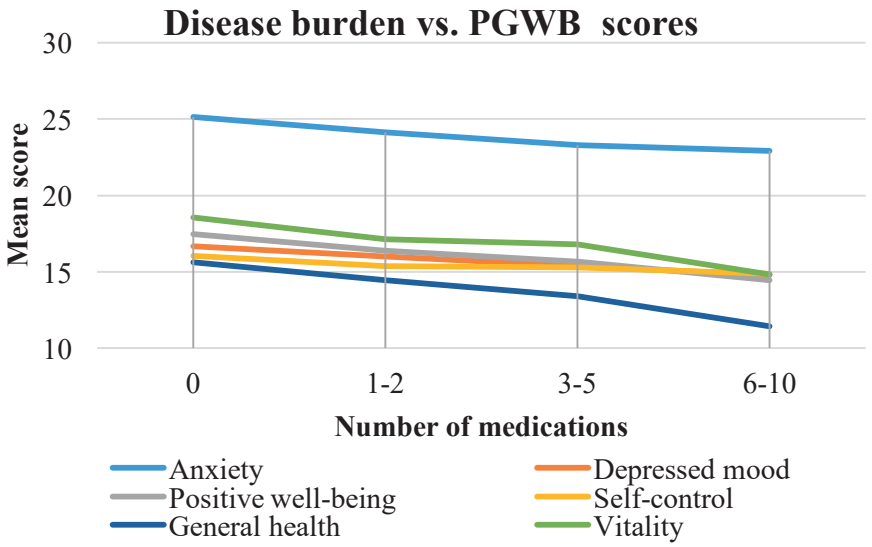

Figure 14. Relationship between HRQoL measured with the PGWB and disease burden. UNIANOVA model $p<0.01$ in all subscales.

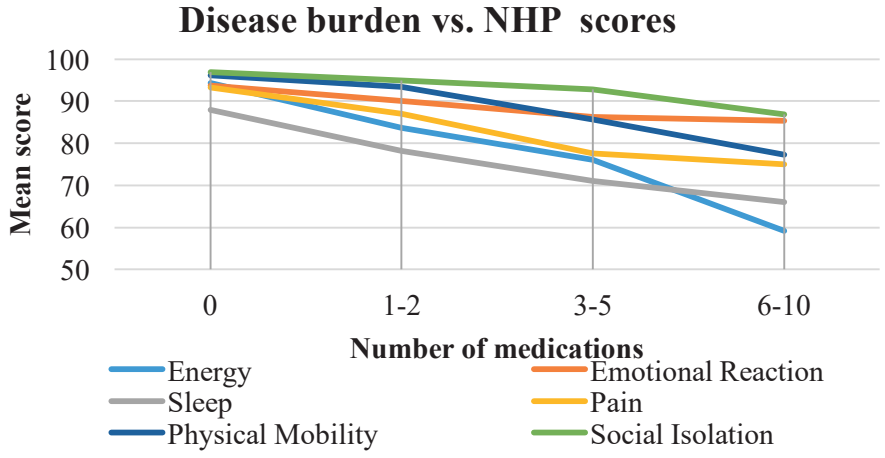

Figure 15. Relationship between HRQoL measured with the NHP and disease burden. UNIANOVA model $p<0.01$ in all subscales. NHP scores are reversed (here high score=high HRQoL) to ease comparison with the other instruments.

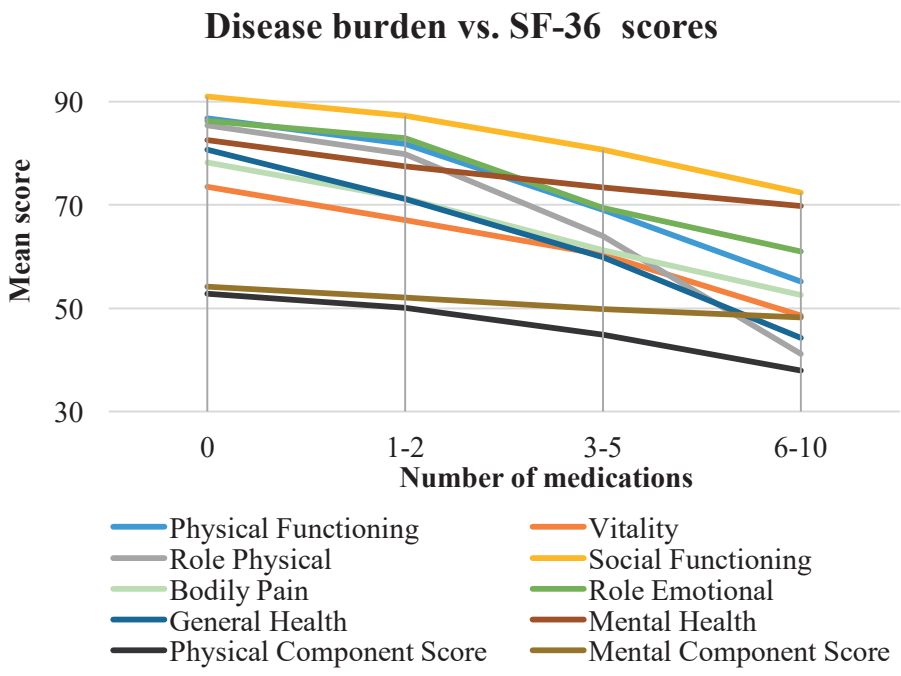

Figure 16. Relationship between HRQoL measured with the SF-36 and disease burden. UNIANOVA model p<0.01 in all subscales.

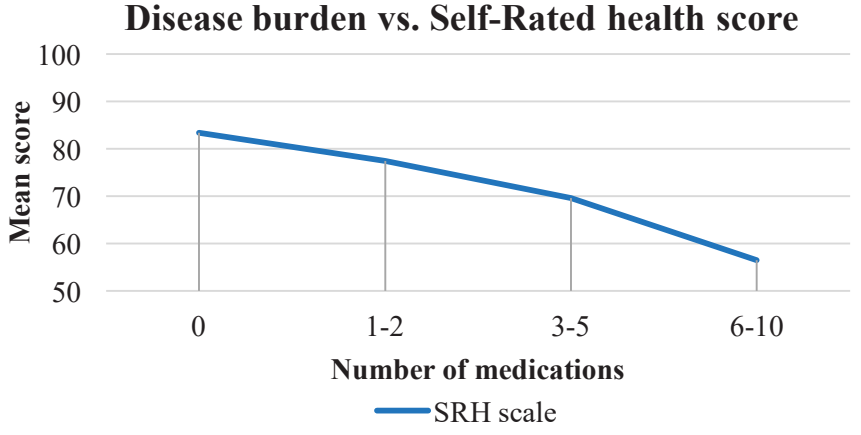

Figure 17. Relationship between HRQoL measured with the Self-rated health scale and disease burden. UNIANOVA model p<0.01. Median score = 80.

Comments on paper IV

Since we make comparisons between the clinical patient groups and population samples, it is important that the HRQoL instruments used are reliable and valid in the population. There are not many studies that apply different instruments in population samples and compare the outcomes.[105,173-175] The aim was to compare the internal consistency of scores, to assess the discriminative ability of the outcome measures and to assess the extent of agreement between the different instruments. By doing so, we hoped to confirm that the instruments performed acceptably so that the comparisons made between the HRQoL in the general population and the patient groups in this thesis were valid. The results presented here and in paper IV support the hypothesis that the HRQoL instruments used are valid and can differentiate the presence of ill-health.

The HRQoL instruments used in this thesis showed both an acceptable internal consistency and discriminative ability. The SF-36 and the PGWB performed equally well and both performed slightly better than the NHP regarding internal consistency and prominence of ceiling/floor effects in this sample. All of the instruments were sensitive, *i.e.* they differentiated between individuals with poor and good health.

The sub-scales of the different instruments measuring similar HRQoL domains showed strong associations with one another, except in the Social functioning domain when applied in the population sample. This may reflect their differences in content: The SF-36 explores the connection between social interactions and the presence of physical and mental symptoms, while the NHP includes five questions specifically on loneliness, social interactions, close friends, and the feeling of being a burden to others, but without the connection to physical or mental symptoms.

The SRH scale correlated significantly, not only with similar sub-scales in the General Health domain, but with *all* the other instruments' sub-scales. This makes it a useful tool for measuring overall HRQoL even in general population samples.[176] It is brief and easy to complete so it is useful when time and resources are limited. However, a single item SRH measurement cannot be seen as a substitute for multi-item

questionnaires when more specific information about specific domains are required, such as mental functioning, sleep or pain etc.

Limitations, paper IV

The participation rate was high but the generalizability of the sample is affected by the inclusion of a subset of the original study group from 1995 which resulted in a study population of middle-aged and elderly subjects. The cross-sectional design made it impossible to report on the responsiveness and test-retest reliability of the instruments, which are both important criteria when evaluating an HRQoL instrument.

GENERAL DISCUSSION

In these studies, GH treatment was effective: the women with TS who had received GH in childhood were on average almost 6 cm taller than the women who had not. GH treatment's effect on bone mass was also favorable in the women with postmenopausal osteoporosis. Neither patient group was GH-deficient, but both were characterized by ovarian failure with ongoing HRT. Both groups were monitored closely, annually to every 5th year, during the follow-up time of 10-20 years, and results were compared to a reference population of women of similar age from the general population.

Despite GH's efficacy in these patients, no significant difference was seen in repeated HRQoL assessment using generic HRQOL instruments during the follow-up time in either patient group after discontinuation of GH treatment. There was no difference in HRQoL during the GH treatment vs. placebo in women with postmenopausal osteoporosis either. Considering this lack of difference, the HRQoL instruments were applied in a population sample in study IV to ensure that the HRQoL instruments used were reliable and valid. They all showed adequate internal consistency and convergent validity. In addition, all four instruments were sensitive to the presence of ill-health. Furthermore, these questionnaires were among the most commonly used for estimating QoL worldwide at the time of initiation of the present studies in the mid-1990s. The present results must lead us to openly discuss the efficiency of GH treatment for the treatment indications evaluated in this thesis.

The current treatment indication for GH treatment of girls with TS is to increase their height on the assumption that being short reduces QoL in childhood as well as in adulthood.[41,148] However, placebo-controlled trials with patient-reported outcomes have not been performed, and height has not been convincingly shown to be a determinant for QoL later in life in subjects with or without TS.[135,142,146](I, II) On the other hand, there are factors (other than height) which *have* repeatedly been shown to affect HRQoL in TS as a whole, like the importance of an early diagnosis, hearing loss, age-appropriate puberty induction and continued HRT, and the availability of pedagogical and physiological support in child- and adulthood.[41](I, II) It is also important to point out

that hearing loss, cardiovascular disease and infertility at young age are all factors that also affect subjects without TS syndrome as well.[177](II) Women with TS would perhaps be better served if the resources allotted to increasing height with GH in all girls with TS were re-assigned to ensure an individualized treatment during childhood and puberty. Regular follow-up throughout these women's lives and treatment of the somatic and possible psychological consequences of the syndrome is essential.

GH has not been approved as a treatment for osteoporosis largely out of concern for safety and because it was costly. An increased risk for prostate, breast and colon cancer has been associated with heightened levels of circulating IGF-1, reviewed by Rosen CJ & Wüster C.[178] Instead, a PTH analogue (teriparatide) is currently the only recommended anabolic treatment option for patients with severe osteoporosis. Even if the sample size was small in study III, no increased mortality was attributable to the treatment 7 years after GH discontinuation in women with postmenopausal osteoporosis. The increase in BMD, BMC and muscle mass during GH treatment were considerable. The decrease in fracture incidence during the follow-up time was most likely due to regular counseling, encouraging lifestyle interventions, and treatment with HRT and/or other bone specific agents. The bone specific treatment was probably the dominating reason behind the maintained beneficial effect on bone mass, since the use of HRT declined dramatically worldwide after the Women's Health Initiative study.[179] There was no association between HRQoL and the presence of osteoporosis compared to the reference population. Nor was there an association between repeatedly assessed HRQoL and GH treatment during the entire follow-up time. This may be because of the even distribution of fractures in the treatment arms of the trial, since it is fracture that is most obviously associated with HRQoL, or the lack of power to detect small differences between the treatment groups.[32,109,162] Perhaps the most striking result of the study is the fracture incidence in the reference population during follow-up (32%) and their under-treatment – only 5% had bone-specific treatment. This problem is, unfortunately still very relevant today and a more active treatment of osteoporosis is essential.[172,180]

It would be of great interest to study the effect of previous GH treatment during childhood in the women with TS with regard to fracture and bone mass outcomes when they are now entering their 40s. Previous findings from 1999, showed a higher fracture prevalence in TS > 45 years of age than in the population.[181] Will the younger generation of TS who have received modern treatment with growth promoting agents, age-appropriate puberty induction and ongoing HRT have a reduced risk of developing osteoporosis and fracture? If there is an association between bone outcomes and previous GH treatment, it may prompt an expansion or alteration to the current GH treatment indication in girls with TS.

The use of non-disease specific HRQoL instruments may limit the conclusions drawn here, but the PGWB, the NHP and the SF-36 questionnaires are all well established, validated and sensitive generic questionnaires.[14,24,109,112] The empirical evaluation of the instruments in a population sample with high a participation rate (62%) further elucidate the relevancy of these instruments.(IV) Furthermore, they were administered repeatedly in the patient groups. When studies I-III were initiated in the mid-1990s, the NHP, PGWB and SF-36 were chosen with care to reflect problems common the patient groups and are all still used in the HRQoL literature.

CONCLUSIONS AND CLINICAL IMPLICATIONS

- Previous GH treatment and adult height were not associated with an improved HRQoL after up to 20 years of follow-up in women with TS when measured using two generic HRQoL instruments, despite a mean 6 cm taller adult height.

- Women with TS are vulnerable to social isolation compared to women in the population so it is important to encourage contact with a psychologist and/or support groups when appropriate.

- GH treatment was beneficial for bone and fracture outcomes after 10 years but did not affect HRQoL in women with postmenopausal osteoporosis. The fracture prevalence decreased in treated women with osteoporosis and increased in the general population at the 10-year follow-up – a sign that there was a noteworthy under-treatment of osteoporosis with bone-specific agents in the community.

- HRQoL in women with postmenopausal osteoporosis was similar to women in the general population which may be a result of the special care and treatment the patients received.

- The generic HRQoL instruments used performed acceptably when applied in the population sample. A simple SRH scale ranging 0-100 could be considered when time and resource efficiency are required.

FUTURE PERSPECTIVES

- Bone and fracture outcomes related to GH and HRT treatments in women with TS needs further research. GH treatment (or other anabolic hormonal treatment like PTH) may be applicable to women with TS who have osteoporosis, of whom the majority have continuous HRT due to ovarian dysgenesis.

- Explore individualizing GH and hormonal treatment to girls with TS to a greater degree by giving GH only to the girls with TS who have a projected height in the very shortest range.

- A TS specific HRQoL instrument could elucidate the issues specific to TS women on the group level.

- A more widespread treatment of osteoporosis in the population needs to be encouraged, especially with anabolic agents like teriparatide (PTH analogue).

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