

Classic Cardiovascular Risk Factors improve in Very Elderly Hypopituitary Patients Treated on Standard Hormone Replacement in Long Term Follow- Up.

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Abstract

Background

Hypopituitarism in the elderly population is an underdiagnosed condition and may increase comorbidities related to glucose metabolism, dyslipidemia, and cardiovascular risk factors. Optimization of hormone replacement take into account alterations in clearance rates of hormones, interaction with other medications, and evaluation of the risk-benefit ratio of treatment is a big challenge for clinical practice.

Objectives

This study aimed to evaluate classic cardiovascular risk factors in hypopituitary septuagenarians and octagenarians by diagnosis and after long-term hormone replacement.

Methods

This is a retrospective observational study, and patients were recruited and selected from a registry in a tertiary medical center. We included patients aged from 70-99 years with hypopituitarism, evaluated hormonal and biochemical parameters, cardiovascular risk scores were calculated by diagnosis and compared after long-term follow-up. All patients signed informed consent. Patients' data were compared to a sex and age-matched control group, with long-term geriatric follow up, without endocrine diseases.

Results

Thirty-five patients were included, 16 patients aged 70-75 years (72.61), 12 patients 76-80 years (72.28), 7 patients 81-99 years (89.28). Pituitary macroadenomas were the main cause of hypopituitarism, mean maximal diameter 3.4 cm (2.9- 4.3), and invasive craniopharyngiomas. At the moment of diagnosis, most patients were overweight, and abdominal adiposity was observed in 76.9% of women and 36.4% of men, mostly in octagenarians and nonagenarians. Co-morbidities were frequent, 85.7% presented Hypertension, 37.1% Diabetes, 53.1% low HDL, 51.5% hypertriglyceridemia. Most patients presented more than two combined pituitary deficiencies, hypogonadism in 88.6%, central hypothyroidism 82.9%, GH deficiency in 65.7%, and adrenal insufficiency in 25.7%. Analysis of cardiovascular risk prediction in the total cohort showed that 57.1% of patients presented a reduction in the General Cardiovascular Disease (CVD) Risk Prediction Score and 45.7% in atherosclerotic CVD risk estimated by ACC/AHA 2013 Pooled Cohort Equation, despite being submitted to conventional hormone replacement, during the meantime follow up of 14.5 years. This reduction was not observed in the control group.

Discussion and Conclusion

In this study, aged hypopituitary patients presented a reduction in estimated general CVD risk during long-term follow-up, despite replacement with corticosteroids, levothyroxine, or gonadal steroids. The early diagnosis and treatment of hypopituitarism in the elderly remain challenging. Larger studies should be

performed to assess the risk-benefit ratio of hormone replacement in the metabolic profile in septuagenarian and octogenarian patients.

1. Background

Hypopituitarism in the elderly is a misdiagnosed and underestimated condition, and targeted hormonal replacement is mandatory to minimize metabolic and systemic complications. A Spanish population-based study evaluated the prevalence (45.5 cases 100,00) and incidence (4,2 cases per 100,00) of pituitary deficiencies in the adult population from 18-79 years.¹ However, this study's median age was 50 years old, and epidemiological data in older patients are lacking.

The effects of aging on the endocrine system involve impairment of signaling mechanisms, biorhythms, and target sensitivity, and represent physiological adaptations of senescence.² However, hypopituitarism is a life-threatening condition that may not be neglected and needs to be recognized.³

Clinical presentation is often insidious, and symptoms are generally nonspecific, such as weakness, tiredness, lethargy, general discomfort, loss of appetite and weight, hyponatremia, varying according to the severity of deficient hormones. Unfortunately, the delay in diagnosis is related to the fact that symptoms may be ascribed to aging per se or associated comorbidities.⁴

In most cases, the symptoms are related to the underlying cause. In adult-acquired hypopituitarism, the leading etiological causes are pituitary tumors with supra or para-sellar extensions or their treatment effects.⁴

The incidence of Pituitary Adenomas (PA) increases with age, being present in 15% of autopsies in octogenarians.⁵ Non-Functioning Pituitary Macroadenomas are the most frequent in aged patients, probably as a consequence of the disease's long duration before the appropriate diagnosis. Aggressive Pituitary Tumors in the elderly may appear clinically similar to younger adults, but present challenges for their best management, when considering the presence of other comorbidities.^{6,7}

These lesions can produce defects in the visual field, as bitemporal hemianopsia due to the compression of the optic chiasma, or diplopia related to the invasion of the cavernous sinus and the cranial pair's involvement. Other symptoms associated with tumor growth and local invasion are headache, rhinoliquorrhea due to CSF fistula.^{8,9}

Considering the rise in life expectancy and the improvement in endoscopic endonasal transsphenoidal surgery, more individuals aged > 65 have been submitted to surgery to benefit from debulking procedures. In a recent study, some authors described that elderly patients are more vulnerable to postoperative complications such as fluid and electrolyte imbalance and stroke risk because of their decreased vascular adaptability.¹⁰ The extent of resection has a significant impact on postoperative hypopituitarism.¹⁰

Hypopituitarism involves multiple endocrine axes, and metabolic effects are diverse and systemic. Growth Hormone (GH) deficiency in adults contributes to muscle weakness and decreased bone mass, leading to frequent falls and fractures, increased complications, and mortality.¹¹ It is known to be associated with an unfavorable lipid profile, with increased triglycerides, cholesterol, body fat, and liver steatosis, all of which are associated with an increased incidence of vascular disease.¹²

A recent study demonstrated that hypopituitary patients without GH replacement have more dyslipidemia, but lower homeostasis model assessment (HOMA-IR) and waist/height values and the occurrence of metabolic syndrome was similar to a control group, paired by age, gender, and Body Mass Index (BMI).¹³

Clinical manifestations of Secondary Adrenal Insufficiency are nonspecific, such as lassitude in the early stage, symptoms frequently attributed to disability related to aging. This is an important diagnosis in the elderly and has a significant impact on the immune system, increasing the risk of infections, which could increase complications.¹¹ Severe hyponatremia may be a revealing sign of hypopituitarism after 60 years of age, and its recognition is critical to reducing hospital stay and mortality.^{14,4,15} On the other hand, inadequate steroid replacement may increase comorbidities in glucose metabolism, dyslipidemia, with exacerbation of both cardiovascular disease and metabolic syndrome.^{16,17}

The androgen replacement in older patients is controversial. Some studies have suggested a protective effect of testosterone therapy against CV events in older men.¹⁸ Others have shown a higher risk of myocardial infarction.^{19,20} A recent review has highlighted the main effects of Testosterone on the cardiovascular system, with favorable effects on vasomotion, arterial stiffness, cardiac electrophysiology, contractility, and remodeling.²¹

Some authors have suggested an association between mortality and hypopituitarism than expected for age and sex-matched control population.^{17,22} The recognition of manifestations of endocrine diseases in older patients is essential in the management approach of geriatric patients. Aging leads to considerable physiological changes in renal function, nutritional aspects and may change hormone transport, clearance, and action in older patients². Careful monitoring is essential to achieve therapeutic benefits and minimize the adverse effects of hormone therapy (Figure 1). As life expectancy increases, elderly individuals become candidates for primary and secondary prevention of cardiovascular disease.²³

The aim of this study is to analyze the association between hormone deficiencies, long-term hormone replacement, and classic cardiovascular risk factors and estimated cardiovascular disease risk at first, and recent clinical evaluation, in a sample of septuagenarians, octagenarians, and nonagenarians patients in the long term follow up.

2. Objective

To identify classic cardiovascular and metabolic risk factors in very elderly patients during the treatment of hypopituitarism in the long term follow up.

3. Subjects And Methods

This is a transversal observational study of classic cardiovascular risk factors in aged patients with a confirmed diagnosis of hypopituitarism, compared to the retrospective analysis of the same parameters collected in the moment of diagnosis from the electronic registry. Data were gathered, and individuals were recruited from August 2019 to April 2020 at the Neuroendocrinology Unit of the University Hospital of Brasília, considered as a Pituitary Center of Excellence. The data concerning hypopituitary patients were compared to sex and age-matched control group, without a diagnosis of endocrine diseases or acute cardiac dysfunction, some of them recruited from a geriatric cohort from a private clinic and others from the University Hospital of Brasília (HUB).

3.1- Inclusion and Exclusion Criteria

Patients included in the study were aged >70 years, with periodical clinical follow-ups, presenting the following criteria: (i) confirmed diagnosis of hypopituitarism, considering two or multiple hormone deficiencies (MPHD), (ii) patients with thyrotrophic and adrenocorticotrophic deficiencies with adjusted replacement doses of levothyroxine and glucocorticoids. Exclusion criteria were: (i) patients with active functioning pituitary tumors (Cushing's disease, prolactinoma, acromegaly), (ii) chronic use of supraphysiological doses of corticoids or levothyroxine, (iii) use of cabergoline, bromocriptine, or somatostatin analogs during the long term follow up.

A control group was composed of 90 patients > 70 years old, with long term geriatric follow up, without endocrine diseases, hormonal replacement, or antecedents of acute cardiovascular events. The sample was composed of 40 patients 70-74 years, 31 patients 75-80 years, and 19 patients 80-99 years, followed for at least ten years regularly in a cardiologic private clinic. Comorbidities at first evaluation were hypertension in 78.1 %, Diabetes in 35.2 %, hypercholesterolemia in 60.1%, and hypertriglyceridemia in 35.8% of patients. All control subjects included were conventionally treated by anti-hypertensives and hypolipemiant drugs.

3.2- Clinical and Laboratory Evaluation

Clinical evaluation of study participants comprised weight, height, waist, and Blood Pressure (BP) measurements (mean of three independent measurements), at the moment of the last follow up medical evaluation. All patients were submitted to Magnetic Resonance Imaging (MRI) of the sellar region by diagnosis to determine the etiology of hypopituitarism. Blood samples were drawn in the morning after overnight fast and hormonal evaluation, including GH, prolactin, IGF-1, cortisol, FSH, LH, Testosterone or estradiol, TSH, fT4. Peptides were determined by chemiluminescent immunometric assay (Immulite 2000). A solid-phase enzyme-labeled chemiluminescent immunometric assay was used to measure serum IGF-I with the sample pretreatment on an onboard dilution step (Immulite 2000). Lipids and

glucose serum measurements were determined respectively by hexokinase and IFCC without pyridoxal phosphate and compared to the same parameters by the diagnosis of hypopituitarism.

The criteria for the diagnosis of hypopituitarism were based on Endocrine Society Clinical Practice Guideline¹⁷: adrenal insufficiency was considered when basal cortisol levels $\leq 3 \mu\text{g/dL}$, or in Insulin Tolerance Test (ITT), cortisol $\leq 18 \mu\text{g/dL}$; GH deficiency when GH peak on ITT $\leq 3 \text{ ng/mL}$ or IGF-1 lower than age-matched reference values; prolactin deficiency if lower than reference values; thyrotropic deficiency if $\text{fT4} < 0.8 \text{ ng/dL}$ and low or inappropriate TSH levels.

The treatment of pituitary deficiencies were: Prednisone was administered once daily in the morning, in doses ranging from 2.5-5 mg per day, because formulations of acetate hydrocortisone are not available in our country. Levothyroxin was administered in doses from 1.4-1.6 $\mu\text{g/kg/day}$. Intramuscular formulations containing testosterone enanthate or cypionate were administered every 2 to 3 weeks, no women had estrogen therapy. No patient was submitted to GH replacement. Patients were evaluated each four months, and hemogram, glucose, lipid profile, fT4 , Testosterone, PSA, hepatic and renal functions, during the follow up time. All patients were treated for comorbidities according to validated guidelines.

3.3- Cardiovascular disease risk estimation

The cardiovascular disease risk was estimated using two widely utilized risk scores using data from the period of diagnosis and the last clinical meeting from each patient, evaluated by the same team from the Unit of Endocrinology from University Hospital of Brasília (HUB).

One of the scores adopted was the 10-year General Cardiovascular Disease (CVD) Risk Prediction Score Using Lipids published by the Framingham Heart Study.²⁴ The considered parameters were age, Diabetes, smoking, treated and untreated systolic blood pressure, total cholesterol, HDL cholesterol. The 10-year CVD risk is considered low $< 10\%$, moderate 10-20% and high $> 20\%$. The score provides a 10-year risk prediction, prediction of the following CVDs: coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure.

The atherosclerotic cardiovascular disease (ASCVD) was estimated using the calculator provided by the ACC / AHA Guideline on the Assessment of Cardiovascular Risk in 2013 based on the Pooled Cohort Equations⁽²⁵⁾. The equation estimates a 10-year risk of coronary death or nonfatal myocardial infarction or fatal or nonfatal stroke.²⁵ Both calculators were derived from cohorts without previous atherosclerotic cardiovascular disease. To adapt and standardize the age range of our population, which goes beyond the age allowed by the scores, we used the age of 79 years (maximum age established by the scores) to calculate the patients' risks. The same scores were calculated for a control group age and sex-matched.

3.4- Statistical analysis

Data were analyzed using the IBM SPSS Statistics version 20.0 software (IBM Corp. released in 2011. IBM SPSS Statistics for Mac, Version 20.0. Armonk, NY: IBM Corp). Categorical variables are summarized as number and percentage, whereas numeric variables are summarized as mean \pm standard deviation (SD) and median (min-max) where appropriate. Categorical variables were compared using the Chi-square test. In the comparison of numerical variables between the groups, one-way analysis of variance (ANOVA) was used when assumptions were met, and the Kruskal–Wallis test was used when assumptions were not met. Covariance analysis (ANCOVA) was done to compare the difference between Framingham Risk Score (FRS) at diagnosis and the last clinical meeting from each patient, taking into account time's follow-up as a covariate. A p-value < 0.05 was considered to be statistically significant.

3.5- Ethics Approval

The study complied with the WMA Declaration of Helsinki and its amended versions of ethical principles for medical research involving human subjects. It was approved by the Ethical Committee on Human Subject Research from the Faculty of Health Sciences, University of Brasilia. All patients signed a proper informed consent before participating in the study.

4. Results

From a cohort of 104 patients aged more than 70 years with previously reported pituitary dysfunction in our hospital (incidental findings of intrasellar, parasellar, and suprasellar lesions, clinical investigation of hypopituitarism), thirty-five patients matched the inclusion criteria: sixteen patients aged 70-74 years (72.61y 70-74), twelve patients 75- 80 years (77.28y 75-78), seven patients 81-99 years (89.28 y 81-99). The time of follow up since the diagnosis of hypopituitarism in our clinic was 14.8 (6-18) years. As an underlying cause of hypopituitarism, most patients had pituitary macroadenomas, mean maximal diameter 3.4 cm (2.9- 4.3), craniopharyngiomas with supra, and parasellar extension were also observed (Table 1).

Some patients were submitted to surgery and adjuvant radiotherapy, 20% of patients from 70-74 years presented previous apoplexy. Few patients were previously treated with bromocriptine, cabergoline, or octreotide before diagnosing hypopituitarism (Table 1). All patients with a diagnosis of functioning pituitary tumors matched the criteria of cure for hormone hypersecretion before inclusion in the study.

Hypopituitarism was present in all patients by diagnosis. GH deficiency in 65.7%, hypogonadism in 88.6%, central hypothyroidism in 82.9%, adrenal insufficiency in 25.7%, 94.28 % presented more than two combined deficiencies.

At clinical evaluation by the time of diagnosis of hypopituitarism, most of the patients were overweighted, 25.71% were considered obese. Relative sarcopenia was observed in all patients. Abdominal adiposity was present in 76.92% of women and 39.13 % of men, being more frequent in octogenarians and nonagenarians (table 2).

Comorbidities were frequent by diagnosis, 85.71% presented hypertension, 37.14% diabetes, 62.8% hypercholesterolemia, and 48.57% hypertriglyceridemia. All patients were treated for comorbidities according to validated guidelines and achieved control after three months of medical treatment. (Table 3)

ASCVD algorithm applied by the ACC / AHA

All patients presented high cardiovascular risk scores by diagnosis, but 57.14% of patients presented a reduction estimated 10-year CVD risk during the follow-up of 14.57 years. According to ages, calculated 10-year CVD risk reduced respectively, 66% (70-75 yo), 57.15% (76-80 yo), and 42.85% (81-99 yo), during the long term follow up ($p < 0.003$). No significant reduction in estimated 10-year ASCVD risk was observed (Table 4).

Comparing the hypopituitary patients to the control group, most of the non-endocrine geriatric patients presented an increase in estimated 10-year CVD risk ($p < 0.001$) and also in 10-year ASCVD risk ($p < 0.001$) (Figure 1).

5. Discussion

The diagnosis of hypopituitarism in elderly patients reflects challenges. The presence of clinical comorbidities prevalent in aging may raise concerns about possible complications of replacement with thyroid hormones, glucocorticoids, and sex steroids. Optimization of the individual hormone dosage and long-term monitoring remain a primary clinical goal in hypopituitary patients.²⁶

In this study, the presence of multiple pituitary axis involvements was a relevant finding. The most frequently compromised axis was the gonadotropic, somatotrophic, and thyrotrophic, followed by the adrenocorticotrophic. The main symptoms were related to muscle weakness and tiredness, present among patients' complaints about long periods and attributed, in other medical evaluations, to physical and psychological deterioration related to aging.

Most of the patients analyzed were overweight and abdominal obesity was more frequent in older women. Studies suggest that elderly patients are more prone to malnutrition when clinical and biochemical parameters are analyzed, increasing morbidity and mortality. The Body Mass Index represents low reliability since the increase in adiposity associated with sarcopenia may reflect a normal BMI.²⁷

Atherogenesis results from genetic predisposition and exposure to risk factors, as dyslipidemia, Diabetes, sedentary behavior, smoking, hypertension, and emotional stress. Longevity may represent individuals who have manifested less cardiovascular risk factors during their lifetime. In people aged more than 80 years, the pathogenic puzzle is uncertain, and data is scarce. Some authors have suggested new modulators for atherogenesis as cellular senescence, syndrome of frailty, sarcopenia.^{23,28}

Sarcopenia is a relevant component of senescence and frailty syndrome and may increase the atherogenic process due to the replacement of muscle mass by adipose tissue. This metabolic pathway is an essential player in cardiometabolic health in hypopituitary patients, as the changes in body composition are related to growth hormone deficiency and hypogonadism.^{29,30,31} Some authors have described that sarcopenia has more impact than weight excess in subclinical atherosclerosis in octogenarians.³²

In our study, the very elderly patients presented abdominal fat accumulation, and most of the septuagenarians and octogenarians were considered overweight or obese. In hypopituitarism, trophic hormones for muscle synthesis are insufficient, and adipose tissue gradually replaces muscle tissue and accumulates in the abdominal visceral region. Most of the patients from our cohort presented GH deficiency, but none was submitted to growth hormone replacement.

All hypocortisolemic patients were treated on exogenous standard steroid substitution, that fail to mimic the natural circadian rhythm of cortisol secretion perfectly. Inadequate steroid replacement results in risk exacerbation of both cardiovascular disease and metabolic syndrome.^{33,17}

Hormonal deficiencies can contribute to the worsening of long-term risk factors. Some authors suggest that elderly patients with adrenal insufficiency present a sarcopenia tendency, despite being classified as overweight or obese by the Body Mass Index. Long-term replacement with glucocorticoids, along with the aging process, has a significant impact on changes in body composition, especially in the redistribution of body fat.³⁴ On the cardiovascular system, glucocorticoids enhance vascular reactivity to angiotensin II and norepinephrine through the expression of $\alpha 1B$ and $\beta 2$ receptors, the induction of Ca^{2+} voltage-dependent channels in vascular smooth muscle cells, the induction of Na/K-adenosine triphosphatase (ATPase) in cardiomyocytes.³⁵ Thus, inadequate glucocorticoid replacement could worsen hypertension.

In our study, despite high waist diameter, steroid replacement did not increase classic cardiovascular risk factors. This finding is in accordance with other authors that did not find an increase in adipocytokines in patients with adrenal insufficiency under corticotherapy.³⁶ However, recent studies suggested that testosterone treatment of older men was associated with progression of noncalcified atherosclerotic plaque.³⁷ Most of our patients had a previous diagnosis of hypertension and dyslipidemia, treated conventionally in the long term follow up. No patient from our cohort presented acute cardiovascular events in 14.8 years follow up.

The estimated CVD risk was high in all hypopituitary patients at the time of inclusion in the study, showing a significant reduction in most patients throughout the follow-up, without a negative impact of the chronically administered hormonal replacement. This finding was not observed in the age-matched control group. It is hard to accurately estimate CVD risk in very elderly subjects as these populations were underrepresented in the cohorts from which the risk scores were derived from.³⁸ However, it is remarkable that using a standard reference age in the risk scores, the other metabolic variables changed favorably after years of follow-up of hypopituitary patients.

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In our series, an increase in abdominal adiposity in older women and the presence of Metabolic Syndrome were frequent, in addition to an elevated estimated general CVD and ASCVD by the risk scores at the time of inclusion in the study. Thus, it should be noted that other cardiovascular risk factors not included in the risk scores such as Metabolic Syndrome and Sarcopenia should be considered in the clinical evaluation and require close monitoring to prevent coronary disease during aging.³⁸

In the present study, we demonstrated that elderly hypopituitary patients undergoing adequate replacement therapy with levothyroxine, glucocorticoids, and androgens for a long term, presented favorable clinical outcomes, reflected by longevity, reduced estimated CVD risk, and no record of cardiovascular events in more than 14 years of clinical follow-up. We recognize that a significant limitation of the study is the sample size. However, the underdiagnosis of hypopituitarism in this age group makes our findings relevant and reinforces the relevance of its recognition and optimization of hormone replacement. Another limitation of our study is the lack of adequate cardiovascular risk calculators for the very elderly population, which motivated us to adapt tools better validated in younger populations. Although it turns unprecise our risk prediction, the real-world clinical practice faces the same challenge.

6. Conclusion

In this study, aged hypopituitary patients presented a reduction in estimated CVD risk during long-term follow-up, despite hormone replacement with low-dose glucocorticoids, levothyroxine, or androgens in men. None of them developed acute cardiovascular events in the longterm follow-up. Hormone replacement had no negative impact on cardiovascular and metabolic risk scores in septuagenarian, octogenarian, and nonagenarian hypopituitary patients. Considering the relevance of early diagnosis and the lack of data on medical literature, more extensive studies should be performed to assess the benefit of hormone replacement in metabolic control in older hypopituitary patients.

Abbreviations

HDL- High density Lipoprotein

CVD- General Cardiovascular Disease

ACC/AHA- atherosclerotic cardiovascular disease-American Heart Association

FRS- Framingham Risk Score

ASCVD- Atherosclerotic Cardiovascular Disease

PA- Pituitary Adenomas

CSF- Cerebrospinal Fluid

GH- Growth Hormone

HOMA-IR- homeostasis model assessment -Insulin Resistance

BMI- Body Mass Index

MPHD- Multiple Hormone Deficiencies

BP -Blood Pressure

MRI- Magnetic Resonance Imaging

IGF-1- Insulin Like Growth Factor

FSH – Follicle Stimulating Hormone

LH- Luteinizing Hormone

TSH- Thyrotropic Hormone

fT4- free levothyroxine

IFCC- International Federation of Clinical Chemistry

ITT- Insulin Tolerance Test

HUB- University Hospital of Brasília

SD- Standard Deviation

ANOVA- Analysis of Variance

ANCOVA- Covariance Analysis

ATPase- Adenosine Triphosphatase

Declarations

Ethical Approval and Consent to Participate

The study complied with the WMA Declaration of Helsinki and its amended versions of ethical principles for medical research involving human subjects. It was approved by the Ethical Committee on Human Subject Research from the Faculty of Health Sciences, University of Brasilia. All patients signed a proper informed consent before participating in the study.

Consent for Publication

All patients signed a proper informed consent for publication of the study.

All authors agreed on publication of the study.

Availability of supporting Data

All data is available in electronic records and can be provided if necessary

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Not applicable. This is a retrospective study, and no specific funding was attributed to its development. All data were collected from electronic records.

Competing Interests

Not applicable. The authors declare that they have no competing interests.

Authors Contributions

INR collected all data and was a major contributor in writing the manuscript. AAMS analyzed and interpreted data related to cardiovascular risk estimation. MPR analyzed data and performed statistical tests. LAN was the mentor of the study, and that has hugely contributed to the design of the research, data analysis, and writing the paper.

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Tables

Table 1: Pituitary dysfunctions and treatment by diagnosis

Clinical Characteristics	Ages (years)			P- value
	70-74 (n=16)	75-79 (n=12)	≥80 (n=7)	
Mean age (years)	72.1±1.2	76.3±1.3	89.2±7.0	0.01
Microadenomas (%)	18.8	16.7	0	0.47
Macroadenomas (%)	81.2	83.3	100.0	0.47
NFPA (%)	37.5	50.0	71.4	0.40
Prolactinomas (%)	12.5	25.0	28.6	
Acromegaly (%)	31.2	16.7	0	
Craniopharingiomas (%)	18.8	8.3	0	
Diameter of PA at diagnosis (mm)	22.6±10	26.0±10	25.1±8	0.66
Surgery(%)	43.8	58.3	14.3	0.17
Radiotherapy (%)	12.5	25.0	14.3	0.66

*NFPA (non functioning pituitary adenomas).

Table 2: Clinical characteristics of patients by diagnosis

Clinical Characteristics	Ages (years)				<i>P-value</i>
	Total Cohort (n=35)	70-74 (n=16)	75-79 (n=12)	≥80 (n=7)	
BMI (Kg/m ²)					
<25 (%)	34.3	50.0	33.3	0	
≥25 and <30 (%)	57.1	43.8	66.7	71.4	0.06
≥30 (%)	8.6	6.2	0	28.6	
Waist (cm)					
Ø 88 women (%)	76.9	62.5	100.0	100.0	0.29
Ø 102 men (%)	36.4	50.0	18.2	66.7	0.18
88 women OR 102 men (%)	51.4	56.2	25.0	85.7	0.03
SBP(mmHg)	130	130	136	122	0.45
DBP(mmHg)	79	83	77	75	0.31

* (SBP) Systolic Blood Pressure

* (DBP) Dyastolic Blood Pressure

Table 3: Co-morbidities in Hypopituitary patients

Comorbidities	Age (years)				<i>P-value</i>
	Total (n=35)	70-74 (%) (n=16)	75-79 (%) (n=12)	80-99 (%) (n=7)	
Hypertension* (%)	85.7	93.8	83.3	71.4	0.35
Diabetes** (%)	37.1	43.8	33.3	28.5	0.74
HDL < 40 men/ HDL < 50 women	53.1	64.3	50	33.3	0.42
Hypertriglyceridemia > 150 mg/dL (%)	51.5	57.1	58.3	28.5	0.39
Hypopituitarism (%)					
GH deficiency	65.71	56.2	66.7	85.7	0.39
Hypogonadism	88.6	87.5	83.3	100	0.53
Hypothyroidism	82.9	87.5	83.3	71.4	0.64
Adrenal Insufficiency	25.7	12.5	33.3	42.9	0.23
Multiple Pituitary Hormone Deficiencies (MPHD)					0.52
2 axes	45.7	50	41.7	42.9	
3 axes	28.6	37.5	25	14.3	
4 axes	20	6.2	25	42.9	

*Most patients treated by enalapril and valsartan

** Patients treated by diet, metformin and/or glibenclamide

Table 4: Metabolic Parameters and classic cardiovascular risk factors in long term follow-up

	Diagnosis	Follow-up (14.57 years)	P- value
Body Mass Index (kg/m ²)	27.6 ±4.32	26.8±3.83	0.649
Waist (cm)	102.5 ±10.09	99.4± 10.36	0.004
HDL cholesterol (mg/dL)	46.8 ±13.27	49.3± 11.98	0.159
LDL cholesterol (mg/dL)	112.8 ±33.67	87.7±28.43	0.000
Triglycerides	167.2 ±97.18	125.7 ±38.93	0.023
Fasting Glucose (mg/dL)	116.3 ± 62.58	103.3 ±28.43	0.137
Framingham Score	31.7 ± 20.23	26.3 ±14.07	0.003
Calcium Score	41.6 ±15.6	42.3 ±14.12	0.20

Figures

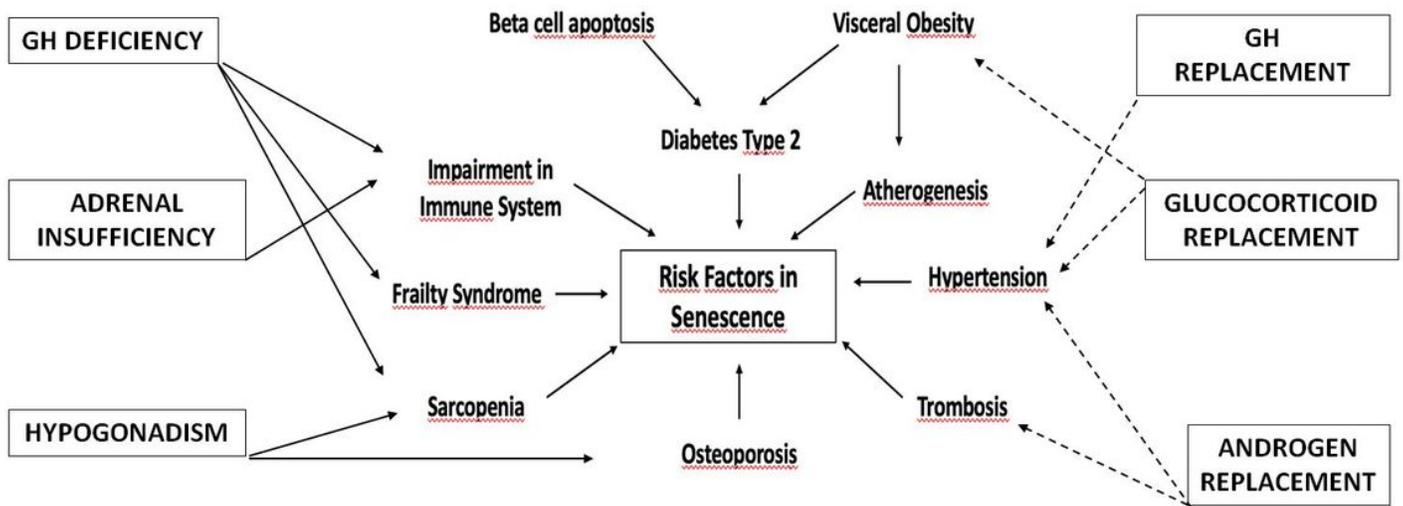


Figure 1

The aim of this study is to analyze the association between hormone deficiencies, long-term hormone replacement, and classic cardiovascular risk factors and estimated cardiovascular disease risk at first,

and recent clinical evaluation, in a sample of septuagenarians, octagenarians, and nonagenarians patients in the long term follow up.

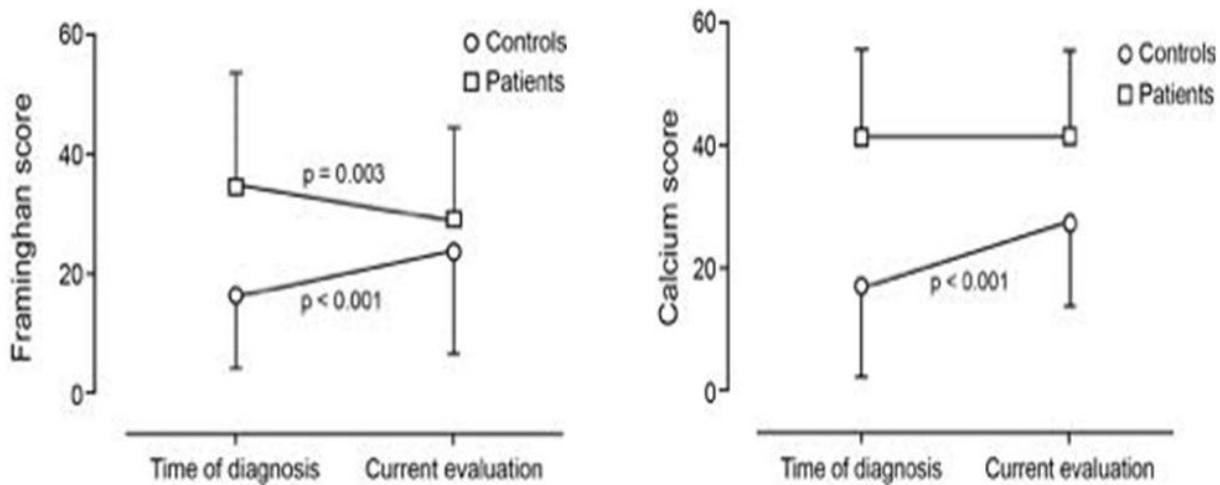


Figure 2

Comparing the hypopituitary patients to the control group