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# FREQUÊNCIA DOS FATORES DE RISCO CARDIOVASCULAR NOS PACIENTES ACROMEGÁLICOS COM DOENÇA CONTROLADA E DESCONTROLADA

Dissertação apresentada ao programa de pós graduação em Ciências Aplicadas À Saúde do Adulto da Faculdade de Medicina da Universidade Federal de Minas Gerais como requisito para a obtenção do grau de mestre

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“A coisa mais indispensável a um homem é reconhecer o uso que deve fazer do seu próprio conhecimento”.

Platão

“Se tens conhecimento, deixa que as outras pessoas acendam as suas velas na tua”

Thomas Fuller

**Resumo :**

Apesar de rara, a acromegalia é uma doença associada a um risco de mortalidade 2 a 4 vezes maior do que aquele da população com mesmo sexo e idade. Esse risco é reduzido quando os pacientes passam a apresentar controle da doença. Além disso, a principal causa de morte nos acromegálicos é cardiovascular e diversos estudos já demonstraram aumento da frequência dos fatores de risco cardiovascular nesses pacientes em comparação à população saudável. Entretanto, muita controvérsia ainda existe a respeito de vários aspectos da acromegalia como a definição do melhor ponto de corte de hormônio do crescimento (GH) que resultaria em controle da doença. Paralelamente a esses fatos, avanços recentes foram feitos e especial ênfase tem sido dada aos aspectos genéticos e moleculares da doença. Todas essas constatações motivaram a realização dessa dissertação na forma de dois artigos. O primeiro artigo teve como objetivo testar a hipótese de que as frequências dos fatores de risco cardiovascular e síndrome metabólica seriam maiores entre os pacientes acromegálicos com doença descontrolada em comparação àqueles com doença controlada. Para tanto, foram avaliados 68 pacientes acompanhados nos ambulatórios de Neuroendocrinologia da Faculdade de Medicina da UFMG, da Santa Casa Belo Horizonte e nos consultórios particulares de Endocrinologia de Belo Horizonte. Os dados foram coletados de Dezembro de 2006 a Dezembro de 2008. Foram dosados nos pacientes do estudo os níveis basais de GH, IGF-1, colesterol total e frações, triglicérides, glicemia em jejum e insulina em jejum. Foram também realizadas

as medidas de cintura, peso, altura e pressão arterial pelo mesmo observador. Os pacientes foram questionados quanto ao hábito tabágico e uso de medicamentos. Apartir dos níveis de GH e IGF-1, os pacientes foram alocados em dois grupos: pacientes com doença controlada: GH <2.0µg/L e IGF-1 normal para idade; e pacientes com doença descontrolada: GH ≥2.0µg/L ou IGF-1 acima da faixa de referência para a idade. Foram avaliadas as frequências de HAS, diabetes mellitus, dislipidemia, síndrome metabólica; e alterações nos valores de referência para homeostasis model assessment of insulin-resistance (HOMA IR), índice de massa corporal (IMC) e cintura nos dois grupos. Trinta e três pacientes (48.52%) apresentavam doença controlada, enquanto 35 pacientes (51.47%) apresentavam doença descontrolada apesar do tratamento. Pela análise univariada, não houve diferença na frequência dos fatores de risco cardiovascular e de síndrome metabólica nos dois grupos. Após análise multivariada, o GH e o IGF-1 se correlacionaram inversamente com o colesterol LDL ($p = 0.012$ e $p = 0.006$ respectivamente) e o HOMA IR se correlacionou diretamente com o IGF-1 ($p = 0.018$). GH também mostrou correlação inversa com a circunferência abdominal (OR = 9.6, CI = 1.1 – 87.1, $p = 0.044$). Os valores de corte de GH <1.0 µg/L e <2.5 µg/L para controle da doença também foram testados como preditores da presença de cada um dos fatores de risco e apresentaram baixa sensibilidade. Uma curva ROC foi realizada para calcular qual valor de GH apresentaria melhor sensibilidade em detectar cada uma das variáveis analisadas. Os valores encontrados variaram entre 0.07 e 0.38µg/L. Concluiu-se que, com os níveis de corte de GH atualmente utilizados, não houve diferença na frequência dos fatores de risco cardiovascular avaliados entre os pacientes com doença controlada e

descontrolada. O segundo artigo foi uma revisão que objetivou avaliar os mais recentes aspectos genéticos e moleculares envolvidos na apresentação e tratamento da acromegalia. Nesse artigo, descrevemos diversas mutações associadas a causas familiares e não familiares de somatotropinomas e descobertas que podem interferir na resposta ao tratamento da doença.

**Palavras chave:** acromegalia, síndrome metabólica, fatores de risco cardiovascular, hipertensão arterial, diabetes mellitus, dislipidemia, obesidade.

**Summary:**

Although rare, acromegaly is a disease that has been associated with a 2- to 4-fold increased mortality risk compared to population with the same age and sex. This risk is reduced when patients achieve disease control. Furthermore, the excess of death has been mainly from cardiovascular causes and many studies have already showed increased cardiovascular risk factors in these patients compared to healthy people. There is a lot of controversy about many issues in acromegaly as the best GH cut off level for disease control. Besides these facts, recent progress has been made and special emphasis has been given to genetic and molecular aspects in acromegaly. All these issues motivated the articles presented in this dissertation. The first article tested the hypothesis that there should be a higher frequency of cardiovascular risk factors and metabolic syndrome in uncontrolled acromegalic patients compared to controlled ones. For this purpose, sixty-eight acromegalic patients were selected from outpatients of the Neuroendocrinololy unit of School of Medicine of Federal University of Minas Gerais, Santa Casa of Belo Horizonte and private offices in Belo Horizonte. Patient assessments were performed from December 2006 to December 2008. After an overnight fast, a peripheral venous blood sample was obtained for the measurement of the following variables: basal GH and IGF-1 levels, lipid profile (total cholesterol, HDL cholesterol, very-low-density lipoprotein - VLDL cholesterol, LDL cholesterol, and triglycerides), plasma glucose and insulin levels. Anthropometric measures (BMI and waist circunference) and blood pressure measurements were performed in all study subjects by the same person. Smoking habit and medications in use were

assessed. According to GH and IGF-1 levels, patients were allocated in two groups: controlled disease (basal GH < 2.0μg/L and IGF-1 in the normal range for age) and uncontrolled disease (basal GH ≥ 2.0μg/L or IGF-1 above the normal range for age). Frequency of hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome and altered homeostasis model assessment of insulin-resistance HOMA IR, BMI and waist circumference were assessed in the two groups. Thirty-three patients (48.52%) had their disease controlled while 35 patients (51.47%) had uncontrolled acromegaly despite having been treated. After univariate analysis, there was no difference in frequency of cardiovascular risk factors and metabolic syndrome between the two groups. After multivariate analysis, GH and IGF-1 correlated inversely with LDL-cholesterol ($p = 0.012$ and $p = 0.006$ respectively) and HOMA IR correlated directly with IGF-1 ($p = 0.018$). GH was also inversely correlated with waist circunference (OR = 9.6, CI = 1.1 – 87.1, $p = 0.044$). GH cut off levels of 1.0μg/L and 2.5μg/L for disease control criteria were also tested but they both showed low sensitivity in predicting the cardiovascular risk factors evaluated and metabolic syndrome. A ROC curve was designed in order to estimate which GH cut off level would show better sensitivity in detecting the presence of each variable evaluated. The GH values ranged between 0.07 and 0.38μg/L, which were very low. We concluded that, with current GH cut off levels for disease control, there was no difference in the frequency of cardiovascular risk factors and metabolic syndrome between controlled and uncontrolled disease groups. The second paper was a review article where we attempted to address the genetic and molecular aspects regarding acromegaly´s presentation and therapeutics. In this article, we assessed the mutations related to familial and non familial

somatotropinomas and also the recent discoveries interfering in the results of treatments.

**Keywords:** acromegaly, metabolic syndrome, cardiovascular risk factors, hypertension, diabetes mellitus, dyslipidemia, obesity.

**Sumário:**

## 1. Considerações Iniciais

Em 1886, Pierre Marie[1] publicou a primeira descrição clínica de uma desordem do crescimento somático e de proporções e a nomeou acromegalia. Posteriormente, Cushing[2], Davidoff[3] e Bailey[4] documentaram as características clínico-patológicas da acromegalia e demonstraram a remissão clínica de seus sinais nos tecidos moles após ressecção do adenoma. Já a associação de um fator hipofisário com o crescimento foi confirmada por Evans e Long que induziram gigantismo em ratos injetados com extratos da hipófise anterior.[5] O estabelelecimento de uma associação inequívoca entre adenoma e acromegalia representou o exemplo mais precoce de uma desordem hipofisária reconhecida clinicamente e tratada com exérese cirúrgica de uma fonte hiperfuncionante.[6,7]

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[1] Marie P. On two cases of acromegaly: marked hypertrophy of the upper and lower limbs and the head. Rev Med. 1886;6:297-333.

[2] Cushing H. The pituitary body and its disorders. Clinical states produced by disorders of the hypophysis cerebri. 1912. JB Lippincott, Philadelphia.

[3] Davidoff LM. Studies in acromegaly III. The anamnesis and symptomatology on one hundred cases. Endocrinology. 1926;10:461-483.

[4] Bailey P, Cushing H. Studies in acromegaly VII. The microscopical structure of the adenomas in acromegalic dyspituitarism (Fugitive acromegaly). Am J Pathol 1928;4(6):545-564.

[5] Evans HM, Long JA. The effect of the anterior lobe of the pituitary administered intra-peritoneally upon growth, maturity and oestrus cycle of the rat. Anat Rev. 1921;21:62.

[6] Sheaves R. A history of acromegaly. Pituitary 1999;2(1):7-28.

[7] de Herder WW. Acromegaly and gigantism in the medical literature. Case descriptions in the era before and the early years after the initial publication of Pierre Marie (1886). Pituitary 2009;12(3):236-44.

A acromegalia é uma doença rara cuja incidência estimada é de 3-4 casos/1 milhão de pessoas. Ela acomete com a mesma frequência homens e mulheres e pode ser diagnosticada em qualquer faixa etária, porém a idade média ao diagnóstico é de 44 anos. Em função do caráter insidioso e da falta de conhecimento por parte da população, o diagnóstico é frequentemente realizado cerca de 7 a 10 anos após o aparecimento dos primeiros sinais e sintomas. Tal fato é extremamente relevante, pois acromegálicos apresentam taxa de mortalidade 2 a 4 vezes maior do que indivíduos da população com mesmo sexo e idade, e um diagnóstico precoce poderia evitar o surgimento de complicações responsáveis pelo aumento da mortalidade.[8]

## 1.1 Secreção e Ação do GH e IGF-1

A secreção de GH é mediada principalmente por dois hormônios hipotalâmicos: o hormônio liberador de hormônio do crescimento (GHRH) e a somatostatina (hormônio inibidor de GH), ambos contribuindo para o padrão episódico de liberação de GH. O GHRH exerce seus efeitos através da ligação a receptores específicos, estimulando a síntese e secreção de GH sendo estes efeitos parcialmente bloqueados pela somatostatina. A ação periférica do hormônio do crescimento é exercida através de sua ligação aos receptores de GH (GHR) encontrados em diversos tecidos, e que, particularmente no fígado, induzem a produção do fator de crescimento insulina-símile (IGF-1). O IGF-1 constitui-se o principal mediador das ações do GH e, por sua vez, promove feedback

[8] Cook D, Ezzat M, Katznelson L et al. AACE Medical Guidelines for Clinical Practice for the diagnosis and treatment of acromegaly. Endocr Pract. 2004;10(3):213-25.

negativo sobre a liberação do GH. Outro importante secretagogo do GH é o hormônio grelina. A grelina é uma proteína produzida predominantemente pelo estômago, apesar de ser expressa em muitos tecidos como o pancreas, o hipotálamo e o sistema cardiovascular. Ela é capaz de estimular a liberação de GH em níveis hipotalâmico e hipofisário e seu efeito orexígeno reforça a relação entre estado metabólico e crescimento.[9] (Fig. 2)

A função primária do GH é promover o crescimento linear. Seus efeitos metabólicos tem como propósito atingir este resultado. O GH, via IGF-1, estimula a captação de aminoácidos e a síntese protéica. Em adição, o GH tende a diminuir o catabolismo protéico via mobilização de gordura. GH em excesso, principalmente a sua exposição crônica, é capaz de reduzir a utilização de carboidratos e diminuir a captação glicose pelas células, promovendo resistência insulínica e hiperinsulinismo.

As propriedades diabetogênicas do GH foram primeiro descritas nos anos 30, quando Houssay mostrou que a hipofisectomia reduziu a hiperglicemia em cães.[10] Estas propriedades foram confirmadas posteriormente quando GH foi administrado em excesso a animais experimentais e humanos. Diversos estudos mostraram que os efeitos antagônicos do GH sobre a ação da insulina se caracterizavam por aumento da gliconeogênese e glicogenólise hepática, e também por uma diminuição na utilização periférica de glicose, que parece estar ligada à um defeito pós-receptor. Além disso, o efeito antagônico do GH

[9] Gahete MD, Durán-Prado M, Luque RM, et al. Understanding the multifactorial control of growth hormone release by somatotropes: lessons from comparative endocrinology. Ann N Y Acad Sci. 2009;1163:137-53.

[10] Houssay BA. The hypophysis and metabolism. N. Engl. J. Med. 1936; 214:961–986.

sobre a ação da insulina também se deve ao efeito lipolítico do GH. Somando-se à resistência insulínica induzida pelo GH, este hormônio também é capaz de exercer efeitos insulinotróficos diretos na célula beta-pancreática.[11]

Os efeitos insulina-símile do IGF-1 foram primeiro descritos por Guler et. al., quando uma única administração de IGF-1 em voluntários saudáveis induziu rapidamente sintomas de hipoglicemia.[12] Posteriormente, Turkalj et al. demonstraram que a terapia com IGF-1 recombinante aumentou a captação periférica de glicose de uma maneira dose-dependente.[13] Em doses hipoglicemiantes equivalentes, infusões de IGF-1 recombinante parecem ser mais potentes em estimular a captação periférica de glicose e menos efetivos em suprimir a produção hepática de glicose comparado à insulina. O efeito insulina-símile do IGF-1 é principalmente devido à sua similaridade estrutural com as moléculas de pró-insulina e insulina. A sinalização do IGF-1 através do seu receptor induz uma cascata de sinalização pós-receptor similar à da insulina. Entretanto, ao contrário da insulina, a biodisponibilidade e bioatividade do IGF-1 são reguladas por uma série de proteínas ligadoras do IGF (IGFBPs). Essas incluem a IGFBP-3, a qual, junto com a unidade ácido lábil, se liga ao IGF-1 na circulação como um complexo ternário; e a IGFBP-1, a qual é inversamente regulada pela insulina. Em contraste, os efeitos do IGF-1 no

[11] Yuen KC, Dunger DB. Impact of treatment with recombinant human GH and IGF-I on visceral adipose tissue and glucose homeostasis in adults. Growth Horm IGF Res. 2006 Jul;16 Suppl A:S55-61.

[12] Guler HP, Zapf J, Froesch ER. Short-term metabolic effects of recombinant human insulin-like growth factor I in healthy adults. N. Engl. J. Med. 1987;317:137–140.

[13] Turkalj I, Keller U, Ninnis R, et al., Effect of increasing doses of recombinant human insulin-like growth factor-I on glucose, lipid, and leucine metabolism in man. J. Clin. Endocrinol. Metab. 1992;75:1186–1191.

tecido adiposo visceral são mais difíceis de avaliar. Parece haver poucos receptores de IGF-1 no tecido adiposo visceral, mas, paradoxalmente, a produção de IGF-1 nesses tecidos é substancial. Estudos têm demonstrado uma associação recíproca entre os níveis de IGF-1 e o tecido adiposo visceral.[14]

## 1.2 Diagnóstico e Tratamento da Acromegalia

A acromegalia é caracterizada pela hipersecreção de hormônio do crescimento (GH). Em mais de 95% dos casos, a fonte de hipersecreção de GH é um adenoma somatotrófico hipofisário, e, mais raramente, por uma doença extra-hipofisária. Nos raros casos familiares, o somatotropinoma pode fazer parte da neoplasia endócrina múltipla tipo 1 (MEN 1), complexo de Carney (CNC), síndrome de McCune-Albright (MAS), somatotropinoma familiar isolado (IFS) ou adenoma hipofisário familiar isolado (FIPA).[15]

O estudo morfofuncional por microscopia eletrônica e imuno-histoquímica permite a separação dos diferentes tipos de adenomas. Os adenomas puros (secretores exclusivos de GH) representam 60% dos somatotropinomas e subdividem-se em densa e esparsamente granulados. Os adenomas densamente granulados apresentam quadro clínico insidioso e, frequentemente, acometem indivíduos acima de 40 anos. Ao contrário, os

[14] Yuen KC, Dunger DB. Impact of treatment with recombinant human GH and IGF-I on visceral adipose tissue and glucose homeostasis in adults. Growth Horm IGF Res. 2006;16(1):55-61.

[15] Cook D, Ezzat M, Katznelson L et al. AACE Medical Guidelines for Clinical Practice for the diagnosis and treatment of acromegaly. Endocr Pract. 2004;10(3):213-25.

esparsamente granulados proliferam rapidamente e são diagnosticados em pacientes mais jovens. Os adenomas mistos (25%), os mamossomatotróficos (10%) e os acidófilos de células-tronco são bi-hormonais, produtores de GH e prolactina. O carcinoma secretor de GH é extremamente raro.[16]

As manifestações clínicas na acromegalia são insidiosas e mudanças na aparência, derivadas do crescimento do esqueleto e aumento de tecidos moles, são responsáveis por apenas 13% das consultas médicas. As alterações faciais incluem lábios e nariz grossos, bossa frontal, crescimento mandibular com prognatismo, alargamento maxilar com afastamento de dentes e má-oclusão. Aumento dos sapatos e anéis também é relatado. Artropatia, uma das complicações clínicas mais comuns, ocorre em 70% dos pacientes e é resultante do espessamento fibroso periarticular. Hipertrofia das glândulas sebáceas e sudoríparas resultam em pele oleosa e excesso de suor. Ainda na pele, podem ser observados acrocórdons, que são pólipos fibroepiteliais, geralmente encontrados no pescoço, tronco e áreas intertriginosas. A presença de três ou mais acrocórdons em pacientes com mais de 50 anos e com história de, pelo menos 10 anos de acromegalia, foi associada à existência de pólipos intestinais. Complicações respiratórias constituem a segunda causa mais frequente de morte na acromegalia. Os pacientes podem apresentar macroglossia, prognatismo, hipertrofia da cartilagem e mucosa laríngea; e o consequente estreitamento de vias aéreas pode gerar apnéia do sono e dificuldade de entubação. Hiperprolactinemia, com ou sem galactorréia, se desenvolve em 30% dos pacientes por compressão da haste ou por co-

[16] Asa SL, Kovacs K. Pituitary pathology in acromegaly. Endocrinol Metab Clin North Am 1992;21:553-74.

secreção pelo tumor e hipopituitarismo pode se apresentar em 40% dos pacientes. A manifestação cardiovascular mais comum da acromegalia é a hipertrofia cardíaca biventricular que se desenvolve independente da hipertensão e se manifesta precocemente. Arritmias cardíacas são documentadas, porém são menos frequentes que as alterações estruturais e funcionais. Extra-sístoles ventriculares, fibrilação atrial paroxística, doença do nó sinusal, taquicardia ventricular e bloqueios de ramo são arritmias comuns em acromegálicos. Colao et al., ao avaliarem as válvulas mitral e aórtica em 64 pacientes acromegálicos e 64 controles, encontraram prevalência mais alta de doença valvular nos pacientes (tanto curados quanto com doença ativa) do que nos controles. A hipertensão arterial é considerada um dos mais importantes fatores prognósticos para mortalidade na acromegalia. Aproximadamente um terço dos pacientes acromegálicos apresenta hipertensão arterial (HAS) e um dos mecanismos que contribui decisivamente para a indução de HAS é o aumento do volume plasmático. Resistência insulínica e diabetes mellitus ocorrem como efeito direto da ação anti-insulina do GH e a frequência de diabetes nos pacientes acromegálicos pode variar de 19-56%. Outras manifestações como déficit visual e cefaléia podem resultar do crescimento tumoral local e constituir a apresentação clínica principal da doença.[17,18,19]

Uma vez suspeitada acromegalia, a dosagem do fator de crescimento insulina-símile 1 (IGF-1) é o próximo passo. Confirmado o aumento de IGF-1 para a

[17] Fedrizzi D, Czepielewski, MA. Distúrbios cardiovasculares na acromegalia. Arq Bras Endocrinol Metab. 2008, vol.52, n.9, pp. 1416-1429.

[18] Colao A, Ferone D, Marzullo P et al. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev. 2004 Feb;25(1):102-52.

[19] Ben-Shlomo A, Melmed S. Acromegaly. Endocrinol Metab Clin North Am. 2008 Mar;37(1):101-22.

idade, a medida do nadir de GH por duas horas após carga de 75 g de glicose é requerida para confirmar o diagnóstico. Com o uso da maioria dos ensaios disponíveis, um nadir menor que 1µg/L exclui a doença. Se não houver supressão adequada do GH, deve ser feita uma ressonância nuclear magnética (RNM). Na ausência de imagem na RNM, deve-se proceder a uma tomografia computadorizada de tórax e abdôme e dosagem de GHRH a fim de localizar uma possível fonte ectópica responsável pela hipersecreção de GH.[20]

O tratamento primário cirúrgico está indicado para microadenomas secretores de GH, assim como para descompressão do efeito de massa sobre estruturas vitais, particularmente o trato óptico.[20] Em geral, aproximadamente 80% dos pacientes portadores de microadenomas e 50% dos que tem macroadenoma normalizam os níveis de IGF-1 após adenomectomia transfenoidal.[21,22] O tratamento medicamentoso é, classicamente, a segunda opção terapêutica na acromegalia, já que em grande percentual de acromegálicos não se obtém cura apenas com a cirurgia. Para tal, dispomos dos agonistas dopaminérgicos, dos análogos da somatostatina e dos antagonistas do receptor de GH.

A ação fisiológica da dopamina sobre o somatotrofo é estimulatória; entretanto, em pacientes acromegálicos, ocorre uma supressão paradoxal da secreção de GH. Os receptores de dopamina pertencem a uma família de receptores acoplados a proteína G e incluem 5 subtipos diferentes de receptor nomeados

[20] Ben-Shlomo A, Melmed S. Acromegaly. Endocrinol Metab Clin North Am. 2008;37(1):101-22.

[21] Ahmed S, Elsheikh M, Stratton IM, et al. Outcome of transphenoidal surgery for acromegaly and its relationship to surgical experience. Clin Endocrinol (Oxf). 1999;50(5):561–7.

[22] Laws ER, Vance ML, Thapar K. Pituitary surgery for the management of acromegaly. Horm Res. 2000;53(3):71–5.

$D_1$-$D_5$. Os agonistas dopaminérgicos se ligam a receptores $D_2$ na hipófise, promovendo a inibição da secreção de GH.[23] Os pacientes com maior benefício dessa opção terapêutica são aqueles nos quais ocorre co-secreção de prolactina pelo tumor.

O primeiro agonista dopaminérgico disponível na prática clínica foi a bromocriptina. No entanto, o controle laboratorial da acromegalia com esta droga é modesto. Uma revisão de 31 estudos mostrou que foram alcançados níveis de GH < 5 µg/L em 20% dos pacientes e o IGF-1 normalizou-se em 10%.[24] A cabergolina é um agonista dopaminérgico com alta afinidade pelos receptores $D_2$ que reduziu os níveis de GH para menos de 2µg/L e normalizou IGF-1 em aproximadamente 30 % dos pacientes.[25]

Os análogos do receptor de somatostatina são atualmente a farmacoterapia de escolha para tratamento clínico da acromegalia. Os análogos de somatostatina exercem seus efeitos através da ligação aos receptores de somatostatina (SSTR) localizados na membrana celular. Cinco subtipos de receptor foram descritos ($SSTR_{1-5}$). Duas formulações de análogos da somatostatina estão disponíveis para o tratamento da acromegalia; o octreotide e o lanreotide. Ambos se ligam aos receptores de somatostatina subtipo 2 (SST2) com alta afinidade e, em menor extensão, ao SST5, enquanto o octreotide também

[23] Pivonello R, Ferone D, Lombardi G, Colao A, Lamberts SW, Hofland LJ. Novel insights in dopamine receptor physiology**.** Eur J Endocrinol. 2007;156(1):13-21.

[24] Colao A, Ferone D, Marzullo P, et al. Effect of different dopaminergic agents in the treatment of acromegaly. J Clin Endocrinol Metab. 1997;82(2):518–23.

[25] Abs R, Verhelst J, Maiter D, et al. Cabergoline in the treatment of acromegaly: a study in 64 patients. J Clin Endocrinol Metab. 1998;83(2):374–8.

exibe alguma afinidade ao SST3. O Sandostatin LAR Depot é um composto de octreotide com longa ação administrado de forma intramuscular de 4 em 4 semanas. A maioria dos estudos avaliando a eficácia dos análogos de somatostatina definiu controle de doença por meio de GH basal menor do que 2,5µg/L e IGF-1 normal para idade e sexo.[26] O Sandostatin LAR suprimiu os níveis de GH e IGF-1 em 65% e 63% dos pacientes respectivamente.[27,28] Esses estudos também demonstraram uma redução de 70% do tumor com Sandostatin LAR. O Pegvisomanto é um antagonista do receptor de GH que interfere com a sinalização do receptor, inibindo a geração de IGF-1. O Pegvisomanto é mais potente que análogos da somatostatina para a inibição da geração periférica de IGF-1. Doses diárias de 40 mg dadas por 12 meses normalizaram os níveis de IGF-1 em 97% dos pacientes.[29] A radioterapia é usualmente reservada para os pacientes com resistência ou recorrência tumoral pós-operatória, ou que são resistentes ou intolerantes ao tratamento medicamentoso.[30]

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[26] Ben-Shlomo A, Melmed S. Somatostatin agonists for treatment of acromegaly. Mol Cell Endocrinol. 2008 May 14;286(1-2):192-8.

[27] Ayuk J, Clayton RN, Holder G, et al. Growth hormone and pituitary radiotherapy, but not serum insulin-like growth factor-I concentrations, predict excess mortality in patients with acromegaly. J Clin Endocrinol Metab. 2004;89(4):1613–7.

[28] Ben-Shlomo A, Melmed S. Acromegaly. Endocrinol Metab Clin North Am. 2008 Mar;37(1):101-22.

[29] Trainer PJ, Drake WM, Katznelson L, et al. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med. 2000;342(16):1171–7.

[30] Ben-Shlomo A, Melmed S. Acromegaly. Endocrinol Metab Clin North Am. 2008 Mar;37(1):101-22.

## 1.3 Fatores de Risco Cardiovascular na Acromegalia

A mortalidade elevada associada à Acromegalia foi demonstrada em estudos epidemiológicos desde 1970. A taxa de mortalidade de acromegálicos é aproximadamente duas vezes mais elevada que a da população geral, levando a uma redução na expectativa de vida de 10 anos. O excesso de mortes se deve predominantemente à doença cardiovascular, cerebrovascular e à doença respiratória. Em 1993, Bates e al. foram os primeiros a demonstrar que a mortalidade estava relacionada à última medida de GH e que o tratamento com redução dos níveis de GH levava à redução da mortalidade. Outros fatores influindo negativamente na mortalidade seriam a presença de hipertensão e diabetes.[31] Com base em evidências atuais, o último GH inferior a 2-2,5µg/L é um melhor preditor de mortalidade do que IGF-1 normal, possivelmente devido à discrepância entre GH e IGF-1 quando GH está em níveis baixos. Existe alguma evidência sugerindo que um corte mais rigoroso (menor que 1µg/L) traria benefícios adicionais, porém mais estudos são necessários.[32,33]

Estudo de Vilar L. et al. demonstrou que, em comparação com os indivíduos controle, pacientes com acromegalia ativa apresentavam níveis significativamente mais altos de glicemia em jejum, colesterol total, colesterol

[31] Bates AS, Van't Hoff W, Jones JM, Clayton RN. An audit of outcome of treatment in acromegaly. Q J Med. 1993;86:293–9.

[32] Holdaway IM, Rajasoorya RC, Gamble GD. Factors influencing mortality in acromegaly. J Clin Endocrinol Metab. 2004;89:667–74.

[33] Ayuk J, Sheppard MC. Does acromegaly enhance mortality? Rev Endocr Metab Disord. 2008;9:33–39.

LDL, colesterol VLDL, triglicérides, lipoproteína a , HOMA IR e fibrinogênio, assim como níveis mais baixos de colesterol HDL e proteína S. Em ambos os grupos, os níveis de homocisteína, antitrombina III, proteína C e proteína C altamente sensível foram similares.[34] Já estudo de Potter et al., comparando 12 pacientes acromegálicos com doença ativa avaliados no tempo zero e 24 semanas após tratamento, 12 pacientes acromegálicos cuja remissão foi alcançada com cirurgia e 12 controles saudáveis mostrou, com 24 semanas de tratamento, níveis mais elevados de resistência insulínica e fibirinogênio nos pacientes com doença ativa comparativamente aos pacientes e sujeitos dos grupos controle; enquanto PCR, leucograma, fator VIII e peptídeo natriurético cerebral (BNP) foram similares nos três grupos.[35]

A adiponectina, um hormônio derivado de adipócitos com atividades anti-aterogênicas e anti-inflamatórias está sabidamente reduzido em pacientes obesos e portadores de outros componentes da Síndrome Metabólica. Em relação aos pacientes acromegálicos, estudo de Lam et al. com 35 pacientes com doença ativa demonstrou hipoadiponectinemia, reversível com o tratamento da doença, provavelmente secundária a hiperinsulinemia.[36] Já Ronchi et al. não encontrou alteração nos níveis de adiponectina nos pacientes acromegálicos e estes níveis não se correlacionaram com os fatores de risco

[34] Vilar L, Naves LA, Costa SS et al. Increase of classic and nonclassic cardiovascular risk factors in patients with acromegaly. 2007;13(4):363-72.

[35] Potter BJ, Beauregard C, Serri O. Serum markers of cardiovascular risk in patients with acromegaly
before and after six months of treatment with octreotide LAR. Pituitary. 2008;11:49–53.

[36] Lam KSL, Xu A, Tan KCB. Serum Adiponectin Is Reduced in Acromegaly and Normalized after Correction of Growth Hormone Excess. J Clin Endocrinol Metab. 2004;89(11):5448–5453

cardiovascular nestes pacientes.[37] Achados de Silha JF. et al. reforçaram a ausência de correlação entre os níveis de adiponectina e a resistência insulínica nos pacientes acromegálicos, apesar dos primeiros se encontrarem elevados nos pacientes do estudo.[38]

### 1.3.1 Hipertensão Arterial na Acromegalia

A hipertensão arterial é considerada um dos fatores prognósticos negativos mais relevantes na mortalidade em acromegálicos. Entretanto, os mecanismos fisiológicos responsáveis pelo aumento da pressão não foram totalmente elucidados. Hipertensão afeta aproximadamente um terço dos pacientes acromegálicos, mas poucos estudos estimaram a prevalência de hipertensão utilizando holter 24 horas e grupo controle não foi incluído nestes estudos.[39] A prevalência de hipertensão nos pacientes acromegálicos variou de 18-60% nas diferenças séries clínicas, com uma prevalência média de 35%. Essa grande variação se deve aos diferentes critérios usados para medir a pressão e definir hipertensão.[40]

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[37] Ronchi CL, Corbetta S, Cappiello V et al. Circulating adiponectin levels and cardiovascular risk factors in acromegalic patients. Eur J Endocrinol. 2004;150(5):663-669.

[38] Silha JV, Ksrek M, Hana V et al. Perturbations in adiponectin, leptin and resistin levels in acromegaly: lack of correlation with insulin resistance. Clinical Endocrinology. 2003 June;58(6):736-742.

[39] Colao A, Ferone D, Marzullo P et al. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev. 2004 Feb;25(1):102-52.

[40] Bondanelli M, Ambrosio MR, degli Uberti EC. Pathogenesis and Prevalence of Hypertension in Acromegaly. Pituitary. 2001;4(4):239-249.

Já foi demonstrado que o sódio (Na) corporal total, água extracelular e volume plasmático estão aumentados na acromegalia ativa e o efeito retentor de Na do GH se correlaciona positivamente com a pressão arterial e o logarítimo do GH nos pacientes não tratados. Após tratamento bem sucedido, a redução do Na se correlacionou, positivamente, com a queda de GH e da pressão. Propôs-se também que a ação celular mediada pelo IGF-1 contribuiria para o efeito retentor de Na via efluxo do mesmo nas células musculares. Com relação ao sistema renina-angiotensina-aldosteona (RAAS), dados conflitantes têm sido publicados. Baixos níveis de atividade de renina-plasmática são usualmente detectados em pacientes acromegálicos normotensos e hipertensos, provavelmente devido à expansão de volume extracelular. Uma diminuição relativa do peptídeo natriurético atrial (PNA) induzida por GH parece contribuir para a reduzida natriurese vista nos pacientes acromegálicos. Resposta inapropriada do PNA à sobrecarga salina também foi observada nestes pacientes. Estudos em animais evidenciaram que a administração de GH e IGF-1 diminuiu a formação de RNAm para PNA em cardiomiócitos. A Acromegalia está frequentemente associada a desordens metabólicas como diabetes mellitus, intolerância oral à glicose e resistência insulínica com hiperinsulinemia, o que pode constituir um fator de risco substancial para o desenvolvimento de hipertensão. É possível que um aumento nos níveis de insulina associado ao excesso de GH possa induzir hipertensão por estimular a reabsorção renal de sódio e a atividade do sistema nervoso simpático. Além disso, a insulina estimula o sistema RAAS e o crescimento das células musculares lisas vasculares; e a resistência insulínica está associada com produção prejudicada de óxido nítrico, ativação prejudicada da bomba de

sódio, e, consequentemente, prejuízo da vasodilatação. Estudos avaliando níveis circulantes de catecolaminas são poucos e contraditórios. Níveis basais de epinefrina, norepinefrina e a excreção de catecolaminas urinárias se encontram dentro dos níveis normais. Estudo de Bondanelli M. et al demonstrou ausência de descenso noturno nos níveis de norepinefrina e pressão arterial em pacientes acromegálico. O excesso de GH é responsável também por uma miocardiopatia específica do paciente acromegálico. No início, a contratilidade e o índice cardíaco aumentam e a resistência vascular periférica diminui. Com o avançar da doença, a fibrose intersticial causa disfunção diastólica e, finalmente, disfunção sistólica. Logo, numa fase inicial, acredita-se que a hipercinesia cardíaca estaria envolvida no mecanismo de hipertensão. GH e IGF-1 podem estar envolvidos na hipertensão arterial também devido aos seus efeitos como promotores de crescimento e seus efeitos no tônus vascular.[41] Os efeitos do tratamento da Acromegalia sobre a hipertensão arterial ainda não estão bem esclarecidos, e os resultados descritos na literatura são conflitantes. Houve redução discreta da pressão arterial sistólica, mas não da diastólica, apenas nos pacientes curados da acromegalia em um grupo de 33 acromegálicos e 33 controles.[42] Em outro estudo, houve redução tanto da pressão sistólica quanto diastólica em acromegálicos com doença controlada e melhora do perfil circadiano em alguns

[41] Bondanelli M, Ambrosio MR, degli Uberti EC. Pathogenesis and Prevalence of Hypertension in Acromegaly. Pituitary. 2001;4(4): 239-249.

[42] Ronchi CL, Varca V, Beck-Peccoz P et al. Comparison between six-year therapy with long-acting somatostatin analogs and successfull surgery in acromegaly: effects on cardiovascular risk factors. J Clin Endocrinol Metabolism. 2006 ;91(1):121-8.

destes pacientes.[43] Uma meta-análise de 18 estudos avaliando o efeito de análogos da somatostatina sobre o coração não encontrou efeito significativo destes sobre o controle da pressão arterial.[44,45]

### 1.3.2 Diabetes mellitus e Resistência Insulínica na Acromegalia

A prevalência de diabetes mellitus nos pacientes acromegálicos é desconhecida, mas varia de 19-56% em diferentes séries. A intolerância oral à glicose só foi avaliada recentemente em 3 estudos diferentes: a prevalência foi de 31% em estudo de Biering et al.[46], 46% no estudo de Kasayama et al.[47] e 16% na análise de Kreze et al.[48] Doses farmacológicas de GH reduzem a utilização da glicose e GH em excesso induz resistência insulínica por prejudicar a habilidade da insulina de suprimir a produção de glicose e de estimular a sua utilização. Sonksen et al. confirmaram a presença de hiperinsulinismo, delineando dois estados intermediários no desenvolvimento

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[43] Minniti G, Moroni C, Jaffrain-Rea ML et al. Marked improvement in cardiovascular function after successful transsphenoidal surgery in acromegalic patients. Clin Endocrinol. 2001;55(3):307-13.

[44] Maison P, Tropeano AI, Macquin-Mavier I et al. Impact of somatostatin analogs on the heart in acromegaly: a metaanalysis. J Clin Endocrinol Metabolism. 2007;92(5):1743-7.

[45] Fedrizzi D, Czepielewski, MA. Distúrbios cardiovasculares na acromegalia. Arq Bras Endocrinol Metab. 2008;2(9):1416-1429.

[46] Biering H, Knappe G, Gerl H et al. Prevalence of diabetes in acromegaly and Cushing syndrome. Acta Med.Austriaca. 2000;27(1):27-31.

[47] Kasayama S, Otsuki M, Takagi M et al. Impaired beta-cell function in the presence of reduced insulin sensitivity determines glucose tolerance status in acromegalic patients. Clin.Endocrinol. 2000;52(5):549-55.

[48] Kreze,A.; Kreze-Spirova,E.; Mikulecky,M. Risk factors for glucose intolerance in active acromegaly. Braz.J.Med.Biol.Res. 2001;34(11):1429-33.

de diabetes na Acromegalia: 1) um estágio hiperinsulinêmico, de tolerância à glicose limítrofe e um pico de insulina mais alto e precoce após carga glicêmica; 2) um estágio caracterizado por uma resposta insulinêmica retardada à sobrecarga de glicose; 3) máxima resposta pancreática em jejum, sem incremento adicional da insulina após sobrecarga glicêmica. Este estágio seria irreversível.[49] Muggeo et al. demonstrou uma ligação anormal da insulina ao seu receptor em monócitos circulantes, o qual se correlacionou com a severidade do excesso de GH, assim como metabolismo alterado de carboidrato e de secreção de insulina.[50] Defeitos pós-receptor também devem ser levados em consideração. Pacientes com acromegalia apresentam uma captação de glicose prejudicada no músculo apesar dos altos níveis de insulina. Delaroudis et al., avaliando 18 pacientes submetidos ao tratamento com análogos da somatostatina, demonstrou que o controle bioquímico incompleto da doença resultou em uma queda significativa dos níveis de glicose, insulina e hemoglobina glicada (HbA1c) nos pacientes acromegálicos.[51] Estudo de Potter et al também evidenciou redução no HOMA após tratamento de 12 acromegálicos com Octreotide LAR.[52] Já estudo com o uso do antagonista do receptor de GH pegvisomanto em 48 pacientes

[49] Sonksen PH, Greenwood FC, Ellis JP. Changes of carbohydrate tolerance in acromegaly with progress of the disease and in response to treatment. J Clin Endocrinol Metab. 1967;27(10):1418-30.

[50] Muggeo M, Bar RS, Roth J et al. The insulin resistance o acromegaly: evidence for two alterations in the insulin receptor on circulating monocytes. J Clin Endocrinol Metab. 1979;48:17-25.

[51] Delaroudis SP, Efstathiadou ZA, Koukoulis,GN et al. Amelioration of cardiovascular risk factors with partial biochemical control of acromegaly. Clin.Endocrinol. 2008;69(2):279-84.

[52] Potter BJ, Beauregard C, Serri O et al. Serum markers of cardiovascular risk in patients with acromegaly before and after six months of treatment with octreotide LAR. Pituitary. 2008;11(1):49-53.

acromegálicos não mostrou redução dos níveis de glicose e insulina.[53] Segundo Baldelli R et al. a intolerância à glicose na acromegalia está associada a altos níveis de microalbuminúria e, por esta razão, esta também deveria fazer parte da avaliação de risco cardiovascular destes pacientes.[54]

### 1.3.3 Lípides na Acromegalia

No início dos anos 70, foi demonstrado que pacientes com acromegalia ativa apresentavam níveis mais baixos de colesterol e níveis elevados de triglicérides.[55] Os níveis de triglicérides se relacionavam com a resistência insulínica nestes pacientes. Diversos estudos dedicaram-se a avaliar o metabolismo lipídico nos acromegálicos, com resultados conflitantes. Os níveis de colesterol foram descritos como normais, elevados, ou até mesmo diminuídos na Acromegalia; a lipoproteína a (Lp-a), as LDL pequenas e densas e os triglicerídeos estavam elevados na maioria dos estudos; e o HDL foi descrito como inalterado ou diminuído. Em uma pequena coorte de pacientes com acromegalia ativa, hiperlipidemia ocorreu em 63%, hiperlipoproteinemia tipo V ocorreu em 13% e hiperlipoproteinemia tipo III em 6%.[56] Maldonado Castro et al. observaram níveis mais altos de Lp-a em pacientes com

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[53] Sesmilo G, Fairfield WP, Katznelson L et al. Cardiovascular risk factors in acromegaly before and after normalization of serum IGF-I levels with the GH antagonist pegvisomant. J.Clin.Endocrinol.Metab. 2002;87(4):1692-9.

[54] Baldelli R, De Marinis L, Bianchi A et al. Microalbuminuria in insulin sensitivity in patients with growth hormone-secreting pituitary tumor. J.Clin.Endocrinol.Metab. 2008;93(3):710-14.

[55] Nikkila EA, Pelkonen R. Serum lipids in acromegaly. Metabolism. 1975;24:829-38.

[56] Takeda R, Tatami R, Ueda K et al. The incidence and pathogenesis of hyperlipidaemia in 16 consecutive acromegalic patients. Acta Endocrinol. 1982;100:358-62.

acromegalia ativa, seguidos pelos pacientes com acromegalia controlada cuja concentração de Lp-a ainda era superior à de indivíduos normais.[57] Estudo de Méstron et al. avaliou 1215 pacientes acromegálicos na Espanha e encontrou uma prevalência de dislipidemia de 25,8%.[58]

O excesso de GH pode induzir diretamente à redução da atividade da lipoproteína lipase (LPL) na acromegalia e um efeito estimulatório do GH na expressão do receptor de LDL no fígado também se mostrou independente dos níveis de IGF-1. Várias anormalidades na composição do HDL em pacientes acromegálicos são consistentes com uma ação prejudicada da lecitina/colesterol acil-transferase (LCAT) e diminuição da proteína transferidora de fosfolípide.[59] Estudo de Vilar et al. encontrou níveis mais altos de triglicérides, colesterol total, colesterol LDL, VLDL, Lp-a e níveis mais baixos de HDL nos pacientes com acromegalia ativa em comparação aos controles.[60] O tratamento da Acromegalia confirmou melhora nos perfil lipídico em diversos estudos.[53] Estudo conduzido por Arosio et al. demonstrou que o tratamento de 20 pacientes acromegálicos com octreotide levou ao aumento dos níveis de HDL e uma redução no LDL e Lp-a. Os pacientes acromegálicos apresentavam partículas de LDL pequenas e densas e este perfil não se modificou durante o

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[57] Maldonado Castro GF, Escobar-Morreale HF, Ortega H et al. Effects of normalization of GH hypersecretion on lipoprotein(a) and other lipoprotein serum levels in acromegaly. Clin.Endocrinol. 2000;53(3):313-19.

[58] Mestron A, Webb SM, Astorga R et al. Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (Registro Espanol de Acromegalia, REA). Eur.J.Endocrinol. 2004;151(4):439-46.

[59] Colao A, Ferone D, Marzullo P et al. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev. 2004;25(1):102-52.

[60] Vilar L, Naves LA, Costa SS et al. Increase of classic and nonclassic cardiovascular risk factors in patients with acromegaly. Endocr Pract. 2007;13(4):363-72.

tratamento.[61] Parkinson et al. avaliaram 22 pacientes com acromegalia ativa submetidos ao tratamento com Pegvisomanto. A normalização dos níveis de IGF-1 resultou em aumento do colesterol total, do LDL e na apolipoproteína B. Apesar de uma queda significante nos níveis de insulina e resistência insulínica, os níveis de triglicérides e HDL não foram afetados pela normalização do IGF-1.[62]

### 1.3.4 Obesidade visceral e Acromegalia

GH e IGF-1 têm papéis importantes na regulação do metabolismo e composição corporal. GH possui efeito lipolítico e é um importante regulador da gordura corpórea. Em níveis supra-fisiológicos, o GH induz resistência insulínica no fígado e músculo. O IGF-1 em contraste, não é lipolítico e possui efeitos insulino-sensibilizantes. Na acromegalia, quando tanto o GH quanto o IGF-1 estão elevados, esta interação é complexa, mas o fenótipo do excesso de GH predomina. Estudo de Freda et al. avaliou a gordura visceral, subcutânea e intramuscular de 24 acromegálicos e 315 adultos saudáveis utilizando ressonância nuclear magnética. As gorduras visceral e subcutânea (principalmente a visceral) se mostraram reduzidas nos pacientes acromegálicos. A proporção de gordura visceral troncular foi menor quanto

[61] Arosio M, Sartore G, Rossi CM et al. LDL physical properties, lipoprotein and Lp(a) levels in acromegalic patients. Effects of octreotide therapy. Italian Multicenter Octreotide Study Group. Atherosclerosis. 2000;151(2):551-57.

[62] Parkinson C, Drake WM, Wieringa G et al. Serum lipoprotein changes following IGF-I normalization using a growth hormone receptor antagonist in acromegaly. Clin.Endocrinol. 2002;56(3):303-11.

maior era a atividade da doença. A gordura intramuscular, entretanto, estava aumentada nos pacientes acromegálicos o que poderia estar relacionado com a resistência insulínica GH-dependente.[63] De acordo com vários estudos epidemiológicos, a gordura visceral – uma combinação de tecido adiposo mesentérico e omental – é o componente adiposo com maior predição de doença cardiovascular e eventos em homens e mulheres mais velhos. Baik et al. estudaram a relação entre gordura corporal e eventos cardiovasculares em 40.000 homens durante 10 anos. Homens com aumento da circunferência abdominal, o qual se correlaciona fortemente com a gordura visceral, apresentaram o maior número de eventos cardiovasculares.[64] Rexrode et al. seguiram, retrospectivamente, 45.000 mulheres durante 8 anos. As mulheres com aumento da circunferência abdominal e com elevada relação cintura/quadril apresentavam um risco de evento coronariano maior do que duas vezes, mesmo após ajuste para hipertensão, diabetes, dislipidemia e mesmo quando o índice de massa corporal (IMC) era normal.[65] Por outro lado, a perda da gordura corporal está associada com redução do risco cardiovascular. Indivíduos com deficiência de GH têm aumento da gordura visceral e perfil lipídico alterado e estão sob maior risco de desenvolver doença cardiovascular. A reposição de GH, com ou sem dieta e exercícios, efetivamente reduz a gordura visceral e melhora o perfil lipídico em adultos

[63] Freda PU, Shen W, Heymsfield SB et al. Lower visceral and subcutaneous but higher intermuscular adipose tissue depots in patients with growth hormone and insulin-like growth factor I excess due to acromegaly. J.Clin.Endocrinol.Metab. 2008;93(6)2334-43.

[64] Inkyung Baik , Ascherio A, Rimm EB et al. Adiposity and mortality in men. Am J Epidemiol. 2000;152(3):264-71.

[65] Rexrode KM, Carey VJ, Hennekens CH et al. Abdominal adiposity and coronary heart disease in women. JAMA 1998; 280:1843–1848.

com deficiência de GH.[66] Em 1989, Salomon et al. publicaram um dos primeiros estudos controle-placebo envolvendo reposição de GH em adultos. Após 6 meses, indivíduos tratados com GH apresentaram um declínio significativo na gordura corporal total comparados ao placebo. Adultos com obesidade central apresentam níveis de GH em 24 horas inferiores a pacientes sem obesidade abdominal.[60] A síndrome metabólica e a deficiência de GH do adulto compartilham muitas similaridades, sendo as características centrais de ambas as síndromes obesidade visceral e resistência insulínica. Em um estudo de Johannsson et al. 30 homens obesos tratados por 9 meses com GH tiveram sua gordura abdominal subcutânea e visceral significativamente reduzida e esse achado foi associado a melhora na resistência insulínica.[67] Doses suprafisiológicas de GH reduzem a gordura visceral, porém prejudicam a resistência insulínica.[68] Estudo de Maison P et al. avaliou 359 homens e 388 mulheres. O IGF-1, neste estudo, mostrou forte correlação positiva com os lípides e correlação negativa com obesidade e glicose. Nas mulheres, o GH mostrou uma forte correlação negativa com a obesidade e glicemia, mas não com os lípides. Nos homens, o GH não estava associado com lípides, obesidade ou glicose.[69]

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[66] Attallah H , Friedlander AL , Hoffman AR. Visceral obesity, impaired glucose tolerance, metabolic syndrome, and growth hormone therapy. Growth Hormone & IGF Research. 2006;16,(1):62-67.

[67] Johannsson G, Marin P, Lonn L et al. Growth hormone treatment of abdominally obese men reduces abdominal fat mass, improves glucose and lipoprotein metabolism, and reduces diastolic blood pressure. J Clin Endocrinol Metab 1997;82:727–734.

[68] Yuen KCJ, Dunger DB. Therapeutic aspects of growth hormone and insulin-like growth factor-I treatment on visceral fat and insulin sensitivity in adults. Diabetes, Obesity and Metabolism. 2007;9:11-22.

[69] Maison P, Balkau B, Souberbielle JC. Evidence for distinct effects of GH and IGF-I in the metabolic syndrome. Diabetic Medicine. 2007;24:1012-1018.

A síndrome de apnéia do sono é comum na Acromegalia e obesidade e ambas doenças estão associadas independentemente com hipertensão e resistência insulínica, contribuindo para a aumentada morbidade e mortalidade. Estudo publicado por Sze et al. avaliou 13 pacientes com acromegalia recém diagnosticada. Quarenta e seis porcento dos pacientes apresentavam apnéia do sono. Os fatores de risco para apnéia do sono foram sexo masculino e longa duração da acromegalia. Após adenomectomia, a síndrome de apnéia do sono foi resolvida em todos os pacientes, independente de acromegalia ter sido curada ou não.[70]

### 1.4 Síndrome Metabólica

O conceito de síndrome metabólica existe por pelo menos 80 anos. Esse conjunto de distúrbios metabólicos, todos fatores de risco para doença cardiovascular, foi primeiro descrito nos anos 20 por Kylin, médico sueco, como o agrupamento de hipertensão, hiperglicemia e gota.[71] Em 1947, Vague chamou atenção para a adiposidade troncular como o fenótipo associado com anormalidades metabólicas, diabetes tipo 2 e doença cardiovascular.[72] Nas últimas duas décadas, houve um aumento importante do número de pessoas com síndrome metabólica. Esse aumento está associado à epidemia global de

[70] Sze L, Schmid C, Bloch KE, Bernays R et al. Effect of transsphenoidal surgery on sleep apnoea in acromegaly. European Journal of Endocrinology. 2007;156(3):321-329.

[71] Kylin E. Studien. Hypertonie-Hyperglykamie-Hyperurikamiesyndrome. Zentralblatt fur innere Medizin (44).1923.

[72] Vague J. La differenciation sexuelle, facteur determinant des formes de l'obesite. Presse Med. 1947;30: 339–40.

obesidade e diabetes. Em 1988, surgiu a iniciativa de desenvolver uma definição reconhecida internacionalmente. Os critérios para definir síndrome metabólica utilizados pela organização mundial de saúde (WHO)[73], National Cholesterol Education Program´s Adult Treatment Panel III (NCEP ATP III)[74] e International Diabetes Federation (IDF)[75] estão enumerados nas tabelas 9, 10, 11 e 11.1. A hipótese unificadora mais aceita para descrever a fisiologia da síndrome metabólica é a resistência insulínica. Um contribuidor importante para o desenvolvimento de resistência insulínica é o excesso de ácidos graxos circulantes. Os ácidos graxos livres (AGL) são liberados pelo excesso de tecido adiposo. No fígado, os AGL aumentam a produção de glicose, triglicerídeos e a secreção de VLDL. Os AGL também reduzem a sensibilidade insulínica no músculo por inibir a captação de glicose mediada por insulina. Defeitos associados incluem uma redução na conversão de glicose a glicogênio e acúmulo de lípides em triglicérides. Aumento nos níveis circulantes de glicose e AGL levam à secreção pancreática excessiva de insulina resultando em hiperinsulinemia. Hiperinsulinemia pode aumentar a reabsorção de sódio e ativação do sistema nervoso simpático, contribuindo para a hipertensão. Associado à resistência insulínica, há o efeito pró-inflamatório parácrino e endócrino dos AGL. Uma variedade de células do tecido adiposo produz interleucina-6 (IL-6) e fator de necrose tumoral α (TNF-α) que, entre outros,

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[73] Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation Diabet Med. 1998;15:539–53.

[74] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.

[75] International Diabetes Federation: The IDF consensus worldwide definition of the metabolic syndrome [artigo online],2005. Disponível em http://www.idf.org/webdata/docs/metac_syndrome_def.pdf.

resultam em mais resistência insulínica e lipólise do tecido adiposo em AGL. Na circulação, IL-6 e outras citocinas aumentam a produção hepática de glicose, a produção de VLDL pelo fígado e a resistência insulínica no músculo. Citocinas e AGL também aumentam a produção de fibrinogênio e inibidor do ativador do plasminogênio 1 (PAI-1) no fígado que complementa a superprodução de PAI-1 pelo tecido adiposo. Isso resulta em um estado pró-trombótico. A redução na produção de adiponectina também encontra-se descrita como estando associada à síndrome metabólica e pode contribuir em sua fisiopatologia.[76] Os critérios para síndrome metabólica foram agrupados para aperfeiçoar a ligação entre resistência insulínica e doença vascular; entretanto, seu papel clínico de prever pessoas sob risco de doença cardiovascular e diabetes permanece incerto. Sattar N. Et al. avaliaram a relação entre síndrome metabólica e o risco de desenvolvimento de eventos cariovasculares e diabetes em 4812 indivíduos do estudo PROSPER (Prospective Study of Pravastatin in the Elderly at Risk)[77] e 2737 do BRHS (British Regional Heart Study).[78] Na análise dos pacientes do estudo PROSPER, a síndrome metabólica não estava associada com risco aumentado de doença cardiovascular nos pacientes sem doença de base, mas estava associada a risco aumentado de diabetes. Nos pacientes do BRHS, síndrome metabólica estava fracamente associada a risco cardiovascular, apesar da forte associação com diabetes. Em ambos os estudos o IMC, a circunferência

[76] Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005;365:1415–28.

[77] Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360:1623–1630.

[78] Walker M, Whincup PH, Shaper AG. The British Regional Heart Study 1975–2004. Int J Epidemiol. 2004;33:1185–1192.

abdominal, triglicérides e glicose não estavam associados com risco cardiovascular, mas todos estavam relacionados com o risco de DM2.[79]

[79] Sattar N, McConnachie A, Shaper AG et al. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. Lancet. 2008;371(9628):1927–1935.

**Hipótese experimental**

Os pacientes com acromegalia descontrolada apresentariam uma maior frequência dos fatores de risco cardiovascular e síndrome metabólica em comparação aos pacientes com doença controlada.

**Hipótese nula**

Não há diferença na frequência dos fatores de risco cardiovascular e síndrome metabólica entre pacientes acromegálicos com doença descontrolada e controlada.

## 2. Objetivo principal:

Avaliar a frequência de fatores de risco cardiovascular e de Síndrome Metabólica nos pacientes acromegálicos com a doença controlada e não controlada; rever os mecanismos genéticos e moleculares envolvidos na origem e tratamento da acromegalia.

## 2.1 Objetivos secundários:

Avaliar se os níveis de GH e IGF-1 se correlacionam com a frequência dos fatores de risco cardiovascular nos pacientes acromegálicos controlados e não controlados

Avaliar se o nível de corte de GH basal utilizado como controle da doença (2µg/L) apresenta boa correlação com os fatores de risco cardiovascular e se há outro nível de corte com melhor sensibilidade e especificidade.

# 3. Cardiovascular Risk Factors and Metabolic Syndrome in Acromegalic Patients with Controlled and Uncontrolled Disease

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## 3.1 Summary

**Background**: Although rare, acromegaly has been associated with a 2- to 3-fold increased mortality.[1-3] Recent findings have suggested that the increased mortality is mainly confined to those with the posttreatment GH levels higher than 2.0µg/L or 2.5µg/L[4-8]. The excess of deaths has been mainly from cardiovascular causes and studies have shown a higher frequency of cardiovascular risk factors in acromegalic patients.

**Objectives**: Evaluate and compare the frequency of cardiovascular risk factors and metabolic syndrome in acromegalic patients with controlled or uncontrolled disease, assess the correlation of GH e IGF-1 levels with the frequency of cardiovascular risk factors, evaluate whether the current basal GH cut-off level for disease control shows good sensitivity in predicting cardiovascular risk factors diagnosis and, if not, which cut-off level would show better sensitivity.

**Methods**: sixty-eight patients with acromegaly were included in this transversal study. Patients were selected from outpatients of the Division of Endocrinology of Federal University of Minas Gerais, Santa Casa of Belo Horizonte and Private Offices in Belo Horizonte, Brazil. All study participants provided informed consent before enrollment. Patients´ assessments were performed from December 2006 to December 2008. Anthropometric measures (BMI and waist circunference) and blood pressure measurements were performed in all study subjects by the same person. Smoking habit and medications in use were recorded. After an overnight fast, a peripheral venous blood sample was obtained for the measurement of the following variables: plasma glucose and

insulin levels, lipid profile (total cholesterol, HDL cholesterol, very-low-density lipoprotein - VLDL cholesterol, LDL cholesterol, and triglycerides), basal GH and IGF-1 levels. According to GH and IGF-1 levels, patients were allocated into two groups: controlled disease (basal GH < 2.0μg/L and IGF-1 in the normal range for age) and uncontrolled disease (basal GH ≥ 2.0μg/L and IGF-1 above the normal range for age). The evaluated variables were blood pressure levels; total, LDL and HDL-cholesterol, triglycerides, diabetes, homeostasis model assessment of insulin-resistance (HOMA IR), waist circunference, body mass index (BMI) and metabolic syndrome.

**Results**: Thirty-three patients (48.52%) had their disease controlled while 35 patients (51.47%) had uncontrolled acromegaly despite having been treated. After univariate analysis, there was no difference in frequency of cardiovascular risk factors and metabolic syndrome between the two groups. After multivariate analysis, GH and IGF-1 correlated inversely with LDL-cholesterol (p = 0.012 and p = 0.006 respectively) and HOMA IR correlated directly with IGF-1 (p = 0.018). We also found that GH was inversely correlated with waist circunference (OR = 9.6, CI = 1.1 – 87.1, p = 0.044). GH cut off levels of 1.0μg/L and 2.5μg/L were also tested but they both showed low sensitivity in predicting the cardiovascular risk factors evaluated and metabolic syndrome. A ROC curve was designed in order to estimate which GH cut off level would show better sensitivity in detecting the presence of each evaluated variable. The GH values found ranged between 0.07 and 0.38μg/L, which were very low.

**Conclusion**: We concluded that, with current GH cut off levels for disease control, there was no difference in the frequency of traditional cardiovascular

risk factors and metabolic syndrome between controlled and uncontrolled disease groups.

**Keywords**: acromegaly, cardiovascular risk factors, hypertension, diabetes, obesity, metabolic syndrome.

## 3.2 Introduction

Acromegaly is a disease of exaggerated somatic growth and distorted proportion. It is characterized by hypersecretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1). In more than 95% of cases, the source of GH hypersecretion is a pituitary somatotroph adenoma and is almost exclusively benign.[9, 10] Although rare (incidence of 3 to 4 cases/million/year), acromegaly is related to a delay of approximately 5 to 10 years in its diagnosis, which may exaggerate the complications due to GH hypersecretion.[10] Acromegaly has been associated with a 2- to 3-fold increased mortality.[1-3] Recent findings have suggested that the increased mortality is mainly confined to those with the posttreatment GH levels higher than 2.0µg/L[11, 12] or 2.5µg/L[4-8]. The excess of deaths has been from cardiovascular, cerebrovascular, or respiratory causes. In the United Kingdom Acromegaly Study, cancer mortality was increased in those with high post-treatment GH levels.[7, 13] However, a recent mortality metaanalysis showed that there is still a slightly increased mortality after biochemical control/cure of acromegaly.[14]

Arterial hypertension is one of the most relevant negative prognostic factors in acromegaly.[15] The prevalence of hypertension in acromegalic patients has been reported to range from 18-60%.[16-32] The pathogenesis of hypertension in acromegaly is unclear and several mechanisms may be involved.[33] Other cardiovascular risk factors, such as altered lipid profile as low levels of high-density lipoprotein (HDL) cholesterol, hypertriglyceridemia and high Lp(a) levels are often present.[34] Impaired glucose tolerance (IGT) and overt diabetes

mellitus are frequently associated with acromegaly.[15] Partial control in disease activity has been described as significant to the improvement of a considerable number of cardiovascular risk markers in acromegaly.[35]

The objectives of this transversal study were to evaluate and compare the frequency of cardiovascular risk factors and metabolic syndrome in acromegalic patients with controlled or uncontrolled disease, to assess the correlation of GH e IGF-1 levels with the frequency of cardiovascular risk factors, evaluate whether the current basal GH cut-off level for disease control shows good sensitivity in predicting cardiovascular risk factors diagnosis and, if not, which cut-off level would show better sensitivity.

**3.3 Methods**

Sixty-eight patients with acromegaly (30 men and 38 women; mean age 50.8 ± 12.8 years) were included in this transversal study. Thirty-three patients (48.52%) had their disease controlled while 35 patients (51.47%) had uncontrolled acromegaly despite having been treated. Patients were selected from outpatients of the Division of Endocrinology of Federal University of Minas Gerais, Santa Casa of Belo Horizonte and Private Offices in Belo Horizonte, Brazil. Patients´ assessments were performed from December 2006 to December 2008.

The diagnosis of acromegaly had been previously confirmed by a failure of GH levels to suppress below 1µg/L during a standard 75g oral glucose tolerance

test (OGTT) associated with increased insulin-like growth factor 1 (IGF-1) values for age. All patients had a nuclear magnetic resonance showing a pituitary adenoma. The patients were allocated into two groups: patients with controlled disease defined as a basal serum GH < 2.0μg/L and normal IGF-1 for age – and uncontrolled disease defined as a basal serum GH ≥ 2.0μg/L or IGF-1 above normal range for age.

Sixteen out of of the controlled patients were using octreotide LAR and twenty four of the uncontrolled patients were being treated with LAR (48.5% vs 68.6%, p = 0.13). Seven out of the controlled patients were receiving cabergoline, while 8 out of the uncontrolled patients were receiving cabergoline (21.1% vs 22.9%, p= 1). Twenty-two uncontrolled patients had been previously submitted to transphenoidal surgery, while 24 of the controlled patients had been submitted to this treatment (62.8% vs 72.7%, p = 0.44). Four uncontrolled patients and 5 controlled patients were submitted to radiotherapy (11.4% vs 15.1%, p = 0.73). Characteristics of the patients are shown in tables 1 and 2.

We excluded patients who had kidney, liver or severe heart failure. Any hormone deficits were being properly replaced except for women in menopause, which were not on estrogen replacement therapy.

Anthropometric measures (BMI and waist-to-rip ratio) were performed in all study subjects by the same person and confirmed by a second observer for agreement. Blood pressure measurements were made twice by the same person with an aneroid sphygmomanometer, with a fifteen minutes interval between the measurements in a relaxed sitting position. Smoking habit and

drugs in use were recorded. After an overnight fast, a peripheral venous blood sample was obtained for the measurement of the following variables: plasma glucose and insulin levels, lipid profile (total cholesterol, HDL cholesterol, very-low-density lipoprotein - VLDL cholesterol, LDL cholesterol, and triglycerides), basal GH and IGF-1 levels. Fasting plasma glucose levels ≥ 126mg/dL, current use of insulin or hypoglycemic agents were classified as diabetes mellitus. The degree of insulin resistance was determined by using the homeostasis model assessment of insulin-resistance – HOMA-IR (HOMA-IR (mmol/L x μU/mL) = fasting glucose (mmol/L) x fasting insulin (μU/mL)/22.5). A value > 2,71mmol/L x μU/mL was considered indicative of insulin resistance[36]. According to the recommendations of the National Cholesterol Education Program Adult Panel III[37], the following cut-off levels for undesirable lipid levels were adopted: total cholesterol ≥ 200mg/dL, LDL cholesterol ≥ 100mg/dL, HDL cholesterol < 40mg/dL for men and < 50mg/dL for women, and triglycerides ≥ 150mg/dL. For metabolic syndrome diagnosis, the National Cholesterol Education Program Adult Panel III[37] recommendation was also followed. The presence of, at least, 3 of the following criteria was necessary to establish the metabolic syndrome diagnosis: waist circunference > 102 cm in men and > 88 cm in women; triglycerides levels > 150mg/dL; HDL cholesterol < 40mg/dL in men and < 50mg/dL in women; blood pressure ≥ 130/85 mmHg and fasting glucose levels ≥ 100mg/dL. Hypertension was diagnosed by the presence of SBP ≥ 140 or DBP ≥ 90 mmHg, or current use of antihypertensive medication. The variables evaluated were blood pressure levels; total, LDL and HDL-cholesterol, triglycerides, fasting glucose levels and diabetes, HOMA IR, waist circunference, BMI and metabolic syndrome.

All assays were performed in duplicate. GH serum levels were measured by a commercial chemiluminescent kit (IMMULITE® 1000, Diagnostic Products Corporation). IGF-1 levels were also determined by a commercial chemiluminescent kit (IMMULITE® 1000, Diagnostic Products Corporation) after extraction from serum with ethanol. Serum total cholesterol, triglycerides, and plasma glucose were measured by VITROS® 3600 Immunodiagnostic System, Johnson & Johnson. LDL cholesterol levels were determined by using the Friedewald equation when the level of triglycerides (TG) was lower than 400mg/dL: LDL = (Total cholesterol – HDL) – TG/5. Insulin levels were determined by chemiluminescent kit (IMMULITE® 2000, Diagnostic Products Corporation).

### 3.4 Ethics

The study was approved by the local Ethics Committee. All study participants provided informed consent before enrollment.

### 3.5 Statistical Analysis

Statistical analysis was performed by SPSS (version 11.0 for Windows; Chicago, IL, USA). Data are reported as mean ± SD, unless otherwise specified. In the analysis of quantitative variables, the Student´s t-test was performed as appropriate. When the number of patients in the groups was small, the non-parametric Mann-Whitney U-test was used. Significance was set at 5%. Categorical variables were compared using the $\chi^2$. Correlations were evaluated by Pearson´s correlation test. Multiple logistic regression and multiple linear analysis was used to determine which variable independently predicted blood pressure levels, diabetes, dyslipidemia, HOMA, obesity and metabolic syndrome, including only those variables which p values were less than 0,25 at the baseline correlation study. A ROC curve analysis was used to determine the best GH level that would predict the presence of the qualitative variables evaluated.

### 3.6 Results

#### 3.6.1 Age, Sex, Blood Pressure, BMI, waist circunference and cigarette smoking.

No statistically significant difference was found between the mean age of patients with uncontrolled acromegaly and the ones with controlled disease (50.7 ±15.1 vs 50.5 ± 10.7 years respectively; p = 0.930). Eighteen patients in

the uncontrolled disease group were male, while 12 patients in the controlled acromegaly group were male (51.4% vs 36.4%; p = 0.314). Twelve patients in the uncontrolled disease group were current smokers, while 7 patients in the controlled acromegalic group were smokers (40% vs 24.1%; p = 0.305).

The mean BMI of the uncontrolled disease group was 28.1 ± 5 kg/$m^2$ and that of controlled disease group was 30.7 ± 5.5 kg/$m^2$ (p = 0.076). After multiple linear regression, age correlated inversely with BMI (standardized β coefficient = - 0.1 p = 0.036). (Table 5)

There was no significant difference in waist circunference between uncontrolled and controlled acromegaly group (97.3 ± 10.1 vs 100.1 ± 11.1 cm; p = 0.543). After multiple logistic regression, waist circunference was directly associated with BMI (OR = 84.5, CI = 5.1 – 140.9, p = 0.002), and inversely associated with GH (OR = 9.6, CI = 1.1 – 87.1, p = 0.044). (Table 6)

Hypertension was found in 19 uncontrolled and in 17 controlled acromegalic patients. (55.9% vs. 56.7%; p = 0.849). (Table 3) There was no statistically difference in mean diastolic blood pressure mean between uncontrolled acromegalics and the controlled ones (0.9 ± 0.1 vs 0.9 ± 0.0; p = 0.821). Otherwise, mean systolic pressure was higher in uncontrolled than controlled patients (131.1 ± 17.6 vs 129.5 ± 20.6 mmHg; p = 0.049). After multiple logistic regression, hypertension was directly associated only with age (OR = 1.04, CI = 1.0 – 1, p = 0.05). (Table 6)

### 3.6.2 Lipid profile

In comparison with the controlled acromegalic group, patients with uncontrolled disease had no difference in mean LDL cholesterol (104.3 ± 35.5 vs 122.3 ± 38.5mg/dL; p = 0.077), mean total cholesterol (181.9 ± 43.4 vs 199.4 ± 46.2mg/dL; p = 0.160), HDL cholesterol (48.9 ± 14 vs 48.8 ± 13.1 mg/dL; p = 0,987) and triglycerides (115.8 ± 43.5 vs 165.1 ± 115.8 mg/dL; p = 0.336). In the group of uncontrolled acromegaly, 8 patients were on statins and in the controlled disease group, 7 patients were in use of statins (22.8% vs 21.2%; p = 0.708). After multiple logistic regression, HDL was inversely associated only with BMI (OR = 1.2, CI = 1.1 – 1.4, p = 0.04). After multiple linear analysis, only BMI correlated directly with triglicerydes (β coefficient = 67.8, p = 0.001), female gender was directly correlated with higher total and LDL-cholesterol levels (β coefficient = 25, p = 0.043 and β coefficient = 18.6, p = 0.001 respectively). LDL-cholesterol was inversely associated with IGF-1 (β coefficient = - 0.05, p = 0.006) and directly with BMI (β coefficient = 2.0, p = 0.016). After multiple logistic regression, LDL-cholesterol was inversely associated with GH (OR = -5.5, CI = -20.9 to – 1.5, p = 0.012). (Tables 5 and 6)

### 3.6.3 Glucose and Insulin Resistance

Mean glucose levels were statistically higher in patients who had uncontrolled disease as compared to controlled acromegalic patients (105.4 ± 22.4 vs 93.3 ± 17mg/dL; p < 0.024). There was no statistically difference in diabetes frequency between uncontrolled patients and controlled patients (20.6% vs 20.0%; p =

0.8) (Table 3). After multiple logistic regression, diabetes mellitus was directly associated only with BMI (OR = 1.2, CI = 1.02 – 1.3, p = 0.03). (Table 6) HOMA IR was > 2.71 in 31.2% of patients who showed uncontrolled disease and in 11.1 % of patients who showed controlled disease (p = 0.214). After multiple logistic regression, HOMA IR was associated only with BMI (OR = 1.3, CI = 1 – 1.6, p = 0.05). (Table 6) After multiple linear regression, HOMA IR was directly correlated with smoking (β coefficient = 2.3, p = 0.012) and IGF-1 (β coefficient = 0.003, p = 0.018). (Table 5)

### 3.6.4 Metabolic Syndrome

Thirteen patients in the group of uncontrolled acromegaly group had metabolic syndrome, while 11 patients in the controlled acromegaly group had metabolic syndrome (38.2% vs 33.3%, p = 0.870). After multiple logistic regression, the presence of metabolic syndrome was associated only with BMI (OR = 1.2, CI = 1.1 – 1.4, p = 0.002).

### 3.6.5 ROC curve

Table 6 shows GH cut offs with 100 % and 90% sensitivity and specificity to detect each evaluated variable. Most part of GH cut off levels that showed 90% of sensitivity were close to the values usually seen in healthy people (0.07 – 0.38 µg/L).[38, 39] Table 7 shows that either GH cut off levels of 1.0, 2.0 or 2.5 have low sensitivity and specificity in predicting the diagnosis of evaluated risk factors.

### 3.7 Discussion

Acromegaly has been associated with a 2- to 3-fold increased mortality which is mainly confined to those with the posttreatment GH concentration higher than 2μg/L [11, 12] or 2.5μg/L[4-8] The excess of deaths has been from cardiovascular, cerebrovascular, or respiratory causes.[13] A mortality metaanalysis showed that there is still a slightly increased mortality after biochemical control/cure of acromegaly.[14] According to these previous data, we would expect that, using the GH cut off level of 2μg/L to define disease control, we could be able to find differences in the frequency of the cardiovascular risk factors evaluated. Instead of that, the results of this study showed that there was no difference in the prevalence of cardiovascular risk factors between controlled and uncontrolled patients. One possible reason for this finding is the similarity between groups. In the uncontrolled group, the patients were being treated in order to reach control and the GH cut off level of 2μg/L is not so strict in the light of the advance of the utilized assays Interestingly, the GH cut off level of 1μg/L was tested and still showed poor sensitivity in diagnosing the evaluated cardiovascular risk factors.

After multiple regression analysis, GH correlated inversely with LDL cholesterol and waist circunference. IGF-1 correlated inversely with LDL cholesterol and directly with HOMA-IR. The other findings were associations of classic cardiovascular risk factors as age with hypertension, BMI with HOMA-IR, waist circunference, triglycerides, diabetes and metabolic syndrome.

Hypertension is considered one of the most important mortality prognostic factors as showed by study of Holdaway IM et al.[40] In our study, 55.9% of uncontrolled acromegalic patients showed hypertension vs. 56.7% in controlled acromegalic group (p = 0.849). Data from the Development Brazilian Index (IDB)[41] showed a prevalence of hypertension in our state of 32.4% in patients with age ranging from 40 to 59 years old, which was lower than that found in the acromegalic patients of our study. The prevalence of hypertension in acromegalic patients has been reported to range from 18 – 60% in different clinical series, with a mean prevalence of about 35%. This large range may be due to the different criteria used to define hypertension and/or the different techniques used for measuring blood pressure.[33] The pathogenesis of hypertension in acromegaly is not clear and several mechanisms may be involved. The sodium and fluid retaining impact of growth hormone (GH) was demonstrated in humans almost 50 years ago and has since then been confirmed in several reports. In our study, although systolic blood pressure was higher in patients with uncontrolled acromegaly, GH did not correlate with hypertension and age was the only variable associated with hypertension.

In our study, despite higher glucose levels in uncontrolled patients, we found a frequency of diabetes of 20.6% in uncontrolled acromegalic patients and of 20% in controlled acromegalic patients. HOMA IR ≥ 2.71mmol/L x μU/mL was found in 31.2% of uncontrolled acromegalic patients and in 11.1% controlled acromegalic patients, but no significant statistically difference was seen between groups. In our study, IGF-1 correlated directly with HOMA-IR. According to Development Brazilian Index (IDB)[41], the prevalence of diabetes

mellitus in our country is 7.60%, lower than seen in the acromegalic patients of our study. BMI was the only variable correlated with diabetes in our study. The prevalence of diabetes mellitus in acromegaly is unknown but ranges from 19-56% in different series. Alternatively, the most well known intermediate form of altered glucose metabolism, referred as impaired glucose tolerance (IGT), has been assessed only recently in three different studies: the prevalence was 31% in a study by Biering et al.[41], 46% in the study by Kasayama et al.[42], and 16% in the analysis by Kreze et al.[43] GH excess is likely to induce a state of insulin resistance, initially manifested as a rise in insulin concentration and an exaggerated insulin response to glucose load. If GH excess remains untreated, fasting hyperglycemia may develop with a fall in fasting insulin, but a more dramatic loss of insulin response to glucose load. Study by Kreze et al. defined a family history of diabetes, female gender and arterial hypertension as additional risk factors for glucose intolerance in active acromegaly.[43]

In our study, LDL levels correlated inversely with GH and IGF-1 and directly with BMI. In our group of patients, after multivariate analysis, female gender was correlated to higher total cholesterol and LDL-cholesterol levels. One possible reason for this finding is that our acromegalic female patients were in their middle-ages and they were not receiving estrogen replacement therapy.

HDL-cholesterol correlated inversely with BMI. Triglycerides correlated directly with BMI. Already in the early 1970s, patients with active acromegaly were shown to have lower cholesterol levels and higher triglyceride levels than in an age-matched control population. The incidence of hypercholesterolemia was similar to that in general population, whereas the incidence of type IV

hypertrygliceridemia was almost three times higher than in controls. Alterations in lipid profile are more evident in patients with concomitant abnormalities in glucose metabolism. GH excess can directly induce the reduction in lipoprotein lipase (LPL) activity in Acromegaly; a stimulatory GH effect on liver LDL-receptor expression has also been proven to be independent of IGF-1 levels. In Acromegaly, both hyperinsulinemia and reduced postheparin lipase activity are among the factors involving in modifying the LDL physical properties, which might also be modified by the hepatic lipase activity that is low in acromegaly.[15] Failure of insulin to suppress lipid oxidation was also observed in the untreated acromegalic patients.[44] Study by Parkinson et al. recently confirmed that successful treatment with pegvisomant in acromegaly increases low baseline serum LDL levels, corroborating the inverse correlation between IGF-1 and LDL-cholesterol found in our study.[45]

Study by Vilar L et al. showed that patients with active acromegaly had significantly higher mean values of total cholesterol, LDL, VLDL, tryglicerides, Lp(a) as well as lower mean levels of HDL.[34] Boero L et al. found that acromegalic patients presented a more atherogenic lipoprotein profile, consisting of higher levels of triglycerides and apolipoprotein B. Cholesteryl ester transfer protein (CETP) activity was significantly increased in acromegalic patients as compared to controls.[46] Study by Maldonado Castro e cols. evaluated 20 acromegalic patients, with either active or controlled disease and 29 healthy subjects as control group. The highest lipoprotein(a) levels were observed in patients with active acromegaly, followed by patients with controlled acromegaly, whose lipoprotein (a) concentrations were still significantly higher

than those of the control group. These findings might suggest that the present biochemical criteria for cure of acromegaly are not strict enough to result in the normalization of all the undesirable metabolic changes found in this disease, and also that significant cardiovascular risk may persist despite succesfull treatment of acromegaly.[47]

Acromegaly consensus statement of 2000 defined cure as a GH nadir after OGTT < 1 mg/L and IGF-1 in the normal range for age and sex.[48] GH assays have evolved since the first studies took place. Dimaraki reported 16 patients with newly diagnosed acromegaly in whom GH and IGF-1 results are discrepant when judged by the consensus criteria. All had an elevated IGF-1, but at least one measure of GH did not fulfilled the consensus criteria.[49] Freda et al performed a 100-g OTTG in 60 postoperative patients with acromegaly. The highest nadir GH level in the control group was 0.13 mg/L and in the patients with active acromegaly GH suppressed as low as 0.33 mg/L.[38] Recent study by Rosario et al suggested GH nadir levels of 0.14 mg/L in healthy men (IFMA Immulite) and 0.40 mg/L in healthy women.[39] Calculation of mean 24-h GH levels is not practicable for the routine care of patients with acromegaly.[50] Recent study by Jayasena et al. found a good correlation between GH basal and GH post OTTG[51], besides OTGG is not validated to assess disease control in patients in use of octreotide LAR.[52] With all these problems, establishing robust guidelines for the diagnosis and assessment of disease activity has been a major challenge.

Our study did not find good sensitivity and specificity of GH levels of 1.0, 2.0 and 2.5µg/L, suggesting a bad performance of these levels in detecting the presence of the evaluated variables. A ROC curve was made and showed values of GH with 90% sensitivity to detect altered variables ranging from 0.07 to 0.38µg/L.

## 3.8 Conclusion

In conclusion, there was no difference in the frequency of cardiovascular risk factors between controlled and uncontrolled acromegalic patients and GH cut off levels used to determine disease status showed bad sensitivity and specificity in diagnosing these variables. According to ROC curve analysis, more strict GH levels would show better sensitivity in detecting the presence of these variables.

## 3.9 Limitations of the study

Acromegaly is a rare disease so studies are usually made with a limited number of patients. Due to the augmented mortality risk of acromegaly, most part of the uncontrolled patients had been treated in order to try to reach disease control. For this reason, the groups were not so discrepant. This fact would make it harder to find differences between groups.

### 3.10 Conflict of interest statement

The authors of this study and School of Medicine of Federal University of Minas Gerais, Brazil have no conflict of interest to declare.

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### 3.13 Tables and Figures

Table 1.
Description and comparison of quantitative variables according to disease status.

| Variable | Disease | | | | | | | | | | | | | p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Uncontrolled | | | | | | | Controlled | | | | | | |
| | N | n* | Mean | SD | Minimal | Maximal | Median | n | n* | Mean | SD | Mínimal | Máximal | Median | |
| Age (years) | 34 | 1 | 50,7 | 15,1 | 18,0 | 80,0 | 49,0 | 31 | 2 | 50,5 | 10,7 | 27,0 | 70,0 | 51,0 | 0,930[1] |
| Total cholesterol | 26 | 9 | 181,9 | 43,4 | 105,0 | 268,0 | 175,0 | 28 | 5 | 199,4 | 46,2 | 99,0 | 272,0 | 192,5 | 0,160[1] |
| LDL | 26 | 9 | 104,3 | 35,4 | 52,0 | 195,0 | 97,0 | 29 | 4 | 122,3 | 38,5 | 35,0 | 190,0 | 119,0 | 0,077[1] |
| HDL | 27 | 8 | 48,9 | 14,0 | 32,0 | 78,0 | 45,0 | 29 | 4 | 48,8 | 13,1 | 22,0 | 79,0 | 48,0 | 0,987[1] |
| TGL | 24 | 11 | 115,8 | 43,5 | 50,0 | 220,0 | 110,5 | 26 | 7 | 165,1 | 115,8 | 41,0 | 503,0 | 123,5 | 0,336[2] |
| Glucose | 30 | 5 | 105,4 | 22,4 | 81,0 | 163,0 | 97,5 | 29 | 4 | 93,3 | 17,0 | 60,0 | 136,0 | 91,0 | **<0,024**[1] |
| Insulin | 18 | 17 | 8,8 | 9,0 | 0,7 | 37,7 | 4,9 | 20 | 13 | 6,0 | 5,7 | 2,0 | 22,8 | 3,2 | 0,129[2] |
| HOMA IR | 16 | 19 | 2,2 | 2,4 | 0,2 | 9,7 | 1,6 | 18 | 15 | 1,3 | 1,4 | 0,4 | 5,6 | 0,5 | 0,175[1] |
| GH | 35 | 0 | 11,5 | 17,8 | 2,06 | 76,9 | 3,7 | 33 | 0 | 0,7 | 0,5 | 0,1 | 1,97 | 0,5 | **0,001**[1] |
| IGF1 | 32 | 3 | 602,3 | 374,6 | 98,9 | 1837,0 | 576,5 | 32 | 1 | 247,7 | 163,9 | 25,0 | 716,0 | 191,0 | **<0,001**[1] |
| BMI | 27 | 8 | 28,1 | 5,0 | 17,5 | 37,5 | 28,4 | 28 | 5 | 30,7 | 5,5 | 23,3 | 42,7 | 30,4 | 0,076[1] |
| Waist (cm) | 22 | 13 | 97,3 | 10,1 | 80,0 | 114,0 | 94,5 | 24 | 9 | 100,1 | 11,1 | 81,0 | 128,0 | 102,0 | 0,543[1] |
| DBP | 21 | 14 | 0,9 | 0,1 | 0,8 | 1,0 | 0,9 | 24 | 9 | 0,9 | 0,0 | 0,8 | 1,1 | 0,9 | 0,821[1] |
| SBP | 33 | 2 | 131,1 | 17,6 | 100,0 | 180,0 | 130,0 | 32 | 1 | 129,5 | 20,6 | 100,0 | 200,0 | 130,0 | **0,049**[2] |

Legend: 1: t-student test; 2: Mann Whitney

Table 2.
Description of patients according to disease status, octreotide LAR use, cabergoline use, statin use, transphenoidal surgery and radiotherapy.

| Variable | Disease | | | | p-value | Total | |
|---|---|---|---|---|---|---|---|
| | Uncontrolled | | Controlled | | | | |
| | n | % | n | % | | N | % |
| Octreotide LAR | | | | | | | |
| Yes | 24 | *68,6* | 16 | *48,5* | 0,13 | 40 | *58,9* |
| No | 11 | *31,4* | 17 | *51,5* | | 28 | *41,1* |
| Cabergoline | | | | | | | |
| Yes | 8 | *22.9* | 7 | *21,1* | 1,0 | 15 | *22,1* |
| No | 27 | *77,1* | 26 | *78,9* | | 53 | *77,9* |
| Transphenoidal surgery | | | | | | | |
| Yes | 22 | *62,8* | 24 | *72,7* | 0,44 | 46 | *67,6* |
| No | 13 | *37,2* | 9 | *27,3* | | 22 | *32,4* |
| Radiotherapy | | | | | | | |
| Yes | 4 | *11,4* | 5 | *15,1* | 0,73 | 9 | *13,2* |
| No | 31 | *88,6* | 28 | *84,9* | | 59 | *86,8* |
| Statin | | | | | | | |
| Yes | 8 | *22,8* | 7 | 21,2 | 0,708 | 15 | *22,1* |
| No | 27 | *77,2* | 26 | 78,8 | | 53 | *77,9* |

Legend: Fisher`s exact test

Table 3.
Description of patients according to disease status, gender, smoking, hypertension and diabetes mellitus

| Variable | Disease | | | | p-value | OR | CI95% | Total | |
|---|---|---|---|---|---|---|---|---|---|
| | Uncontrolled | | Controlled | | | | | | |
| | n | % | n | % | | | | n | % |
| Hypertension | | | | | | | | | |
| Yes | 19 | *55,9* | 17 | *56,7* | 0,849[2] | 1,0 | | 36 | *56,2* |
| No | 15 | *44,1* | 13 | *43,3* | | 1,03 | 0,3 to 3,1 | 28 | *43,8* |
| No information | 1 | - | 3 | - | | - | - | 7 | - |
| Diabetes Mellitus | | | | | | | | | |
| Yes | 7 | *20,6* | 6 | *20,0* | 0,800[2] | 1,04 | 0,6 to 4,1 | 13 | *20,3* |
| No | 27 | *79,4* | 24 | *80,0* | | 1,0 | | 51 | *79,7* |
| Gender | | | | | | | | | |
| Male | 18 | *51,4* | 12 | *36,4* | 0,314[2] | 1,8 | 0,6 to 5,5 | 30 | *44,1* |
| Female | 17 | *48,6* | 21 | *63,6* | | 1,0 | | 38 | *55,9* |
| Smoking | | | | | | | | | |
| Yes | 12 | *40,0* | 7 | *24,1* | 0,305[2] | 2,1 | 0,6 to 7,5 | 19 | *32,2* |
| No | 18 | *60,0* | 22 | *75,9* | | 1,0 | | 40 | *67,8* |
| No information | 5 | - | 4 | - | | - | - | 9 | - |

Legend: [1]: Fisher`s exact test; [2]: Chi-Square test with Yates` correction.

Table 4
Description and comparison of total cholesterol, LDL cholesterol, HDL cholesterol, Triglycerides (TGL), HOMA IR, Waist circunference, BMI and Metabolic syndrome

| Variable | Disease | | | | p-value | OR | IC95% | Total | |
|---|---|---|---|---|---|---|---|---|---|
| | Uncontrolled | | Controlled | | | | | | |
| | n | % | n | % | | | | n | % |
| Cholesterol total | | | | | | | | | |
| < 200 mg/dL | 18 | *69,2* | 15 | *53,6* | 0,368[2] | 2,0 | 0,6 to 7,0 | 33 | *61,1* |
| ≥ 200 mg/dL | 8 | *30,8* | 13 | *46,4* | | 1,0 | | 21 | *38,9* |
| No infomation | 9 | - | 5 | - | | | | 14 | - |
| LDL cholesterol | | | | | | | | | |
| | | | | | 0,086[2] | 3,0 | 0,9 to | | |
| < 100 mg/dL | 15 | *57,7* | 9 | *31,0* | | | 10,7 | 24 | *43,6* |
| ≥ 100 mg/dL | 11 | *42,3* | 20 | *69,0* | | 1,0 | | 31 | *56,4* |
| No information | 9 | - | 4 | - | | | | 13 | - |
| HDL cholesterol | | | | | | | | | |
| ≥ 40 mg/dL in ♂ and ≥ 50 mg/dL in ♀ | 12 | *44,4* | 15 | *51,7* | 0,782[2] | 1,0 | | 27 | *48,2* |
| < 40 mg/dL in ♂ and < 50 mg/dL in ♀ | 15 | *55,6* | 14 | *48,3* | | 1,3 | 0,4 to 4,4 | 29 | *51,8* |
| No information | 8 | - | 4 | - | | | | 12 | - |
| TGL | | | | | | | | | |
| | | | | | 0,294[2] | 2,4 | 0,6 to | | |
| < 150 mg/dL | 19 | *79,2* | 16 | *61,5* | | | 10,2 | 35 | *70,0* |
| ≥ 150 mg/dL | 5 | *20,8* | 10 | *38,5* | | 1,0 | | 15 | *30,0* |
| No information | 11 | - | 7 | - | | | | 18 | - |
| HOMA IR | | | | | | | | | |
| < 2.71 | 11 | *68,8* | 16 | *88,9* | 0,214[1] | | | 27 | *79,4* |
| | | | | | | 3,6 | 0,5 to | | |
| ≥ 2.71 | 5 | *31,2* | 2 | *11,1* | | | 33,6 | 7 | *20,6* |
| No information | 19 | - | 15 | - | | | | 34 | - |
| Waist circunference | | | | | | | | | |
| < 88 cm in ♀ and < 102 cm in ♂ | 10 | *45,5* | 5 | *20,8* | 0,143[2] | 3,2 | 0,7 to 14,2 | 15 | *32,6* |
| ≥ 88 cm in ♀ and ≥ 102 cm in ♂ | 12 | *54,5* | 19 | *79,2* | | 1,0 | | 31 | *67,4* |
| No information | 13 | - | 9 | - | | | | 22 | - |
| BMI | | | | | | | | | |
| < 25 Kg/m$^2$ | 7 | *25,9* | 5 | *17,9* | 0,690[2] | 1,6 | 0,4 to 7,1 | 12 | *21,8* |
| ≥ 25 Kg/m$^2$ | 20 | *74,1* | 23 | *82,1* | | 1,0 | | 43 | *78,2* |
| No information | 8 | - | 5 | - | | | | 13 | - |
| Metabolic syndrome | | | | | | | | | |
| Yes | 13 | *38,2* | 11 | *33,3* | 0,870[2] | 1,2 | 0,7 to 3,8 | 24 | *35,8* |
| No | 21 | *61,8* | 22 | *66,7* | | 1,0 | | 43 | *64,2* |
| No information | 1 | - | 0 | - | | | | 1 | - |

Legend: [1]: Fisher`s exact test; [2]: Chi-Square test with Yates` correction.

Table 5
Multiple linear regression summary

| Variable | Total cholesterol | LDL cholesterol | TGL | BMI | HOMA IR | HDL cholesterol | Waist circunference |
|---|---|---|---|---|---|---|---|
| **Categorical** | | | | | | | |
| Gender | | | | | | | |
| Female | 25,0 (1,4 - 48,6) | 1,0 | --- | --- | --- | --- | |
| Male | 1,0 p = 0.043 | -18,6 (-36,0 to -1,2) p = 0.001 | --- | --- | --- | --- | |
| BMI | | | | | | | |
| < 25 | --- | --- | 1,0 | --- | --- | --- | --- |
| ≥ 25 | --- | --- | 67,8 (2,1 - 133,6) p = 0.001 | --- | --- | --- | --- |
| GH | | | | | | | |
| < 2,0 | --- | --- | --- | --- | --- | --- | --- |
| ≥ 2,0 | --- | --- | --- | --- | --- | --- | --- |
| Smoking | | | | | | | |
| No | --- | --- | --- | --- | --- | --- | --- |
| Yes | --- | --- | --- | --- | 2.3(0.612-4.058) p = 0.012 | --- | --- |
| **Continuous** | | | | | | | |
| Age | --- | --- | --- | -0,1(-0,3 to 0,1) p= 0.036 | --- | --- | --- |
| BMI | --- | 2,0 (0,4 to 3,6) p = 0.016 | --- | --- | --- | --- | --- |
| GH | --- | --- | --- | --- | --- | --- | --- |
| IGF1 | --- | -0,05 (-0,09 to -0,01) p = 0.006 | --- | --- | 0.003(0.001-0.005) p = 0.018 | --- | --- |

Legend: ( ) confidence interval --- Non significant

Table 6
Multiple logistic regression summary

| Variable | Variables – categorical | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Total Cholesterol** | **HDL** | **LDL** | **TGL** | **BMI** | **Waist circunference** | **HOMA** | **Metabolic syndrome** | **Hyperten-sion** | **Diabetes Mellitus** | **Dyslipi-demia** |
| **Categorical** | | | | | | | | | | | |
| Gender | | | | | | | | | | | |
| Female | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Male | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| BMI | | | | | | | | | | | |
| < 25 | --- | --- | --- | --- | --- | 1,0 | --- | --- | --- | --- | --- |
| ≥ 25 | --- | --- | --- | --- | --- | 84,5 (5,1 - 140,9) p = 0.002 | --- | --- | --- | --- | --- |
| GH | | | | | | | | | | | |
| < 2,0 | --- | --- | 5,5 (1,5 - 20,9) | --- | --- | 9,6 (1,1 - 87,1) | --- | --- | --- | --- | --- |
| ≥ 2,0 | --- | --- | 1,0 p = 0.012 | --- | --- | 1,0 p = 0.04 | --- | --- | --- | --- | --- |
| Smoking | | | | | | | | | | | |
| Yes | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Continuous** | | | | | | | | | | | |
| Age | --- | --- | --- | --- | --- | --- | --- | --- | 1,04 (1,0 - 1,1) p = 0.05 | --- | --- |
| BMI | --- | 1,2 (1,1 - 1,4) p = 0.04 | --- | --- | --- | --- | 1,3 (1,0 - 1,6) p = 0.05 | 1,2 (1,1 - 1,4) p = 0.002 | --- | 1,2 (1,02 - 1,3) p = 0.03 | --- |
| GH | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| IGF1 | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |

Legend: ( ) confidence interval OR; --- Non significant

TABLE 7
Area under ROC curve to the variable GH.

| Variable | Area | IC 95% of área | GH values | | | |
|---|---|---|---|---|---|---|
| | | | Sensibility | | Specificity | |
| | | | 100% | 90% | 100% | 90% |
| Total cholesterol | 0,379 | 0,225 -0,532 | 0,07 | 0,12 | 76,90 | 44,10 |
| HDL cholesterol | 0,572 | 0,418 -0,725 | 0,05 | 0,17 | 76,90 | 8,88 |
| LDL cholesterol | 0,288 | 0,150 -0,426 | 0,05 | 0,12 | 53,70 | 44,10 |
| TGL | 0,382 | 0,207 -0,557 | 0,05 | 0,07 | 53,70 | 10,48 |
| BMI | 0,565 | 0,393 -0,737 | 0,08 | 0,30 | 53,70 | 4,81 |
| Waist circunference | 0,400 | 0,224 -0,576 | 0,08 | 0,26 | 48,20 | 8,88 |
| HOMA IR | 0,624 | 0,382 -0,866 | 0,36 | 0,38 | 14,60 | 49,20 |
| Metabolic syndrome | 0,539 | 0,397 -0,681 | 0,07 | 0,36 | 76,90 | 29,70 |
| Hypertension | 0,515 | 0,372 -0,658 | 0,12 | 0,30 | 76,90 | 5,73 |
| Diabetes Mellitus | 0,545 | 0,368 -0,723 | 0,30 | 0,34 | 76,90 | 11,63 |
| Dyslipidemia | 0,498 | 0,311 -0,685 | 0,05 | 0,20 | 77,90 | 44,10 |

TABLE 8
Sensitivity and specificity of GH cut off levels equal to 1,0, 2,0 and 2,5µg/dL in detecting the variables evaluated

| Variable | GH = 1,0 | | GH = 2,0 | | GH = 2,5 | |
|---|---|---|---|---|---|---|
| | Sensitivity | Specificity | Sensitivity | Specificity | Sensitivity | Specificity |
| Total cholesterol | 52,4% | 36,4% | 38,1% | 45,5% | 23,8% | 57,6% |
| HDL cholesterol | 65,5% | 48,1% | 51,7% | 55,6% | 44,8% | 73,7% |
| LDL cholesterol | 48,4% | 29,2% | 35,5% | 37,5% | 22,6% | 73,7% |
| TGL | 53,3% | 37,1% | 33,3% | 45,7% | 20,0% | 57,1% |
| BMI | 55,8% | 33,3% | 46,5% | 41,7% | 41,9% | 83,3% |
| Waist circunf. | 54,8% | 26,7% | 38,7% | 33,3% | 32,3% | 57,3% |
| HOMA IR | 71,4% | 44,4% | 71,4% | 59,3% | 57,1% | 33,3% |
| Metabol. syndrome | 70,8% | 44,2% | 54,2% | 51,2% | 37,5% | 67,5% |
| Hypertension | 63,9% | 35,7% | 52,8% | 46,4% | 38,9% | 57,1% |
| Diabetes Mellitus | 76,9% | 39,2% | 53,8% | 47,1% | 46,2% | 60,8% |
| Dyslipidemia | 59,2% | 41,7% | 49,0% | 50,0% | 34,7% | 50,0% |

# 4. GH-Secreting Pituitary Adenomas: From Molecular Basis to Treatment Options

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## 4.1 Abstract

Acromegaly is a disease of exaggerated somatic growth and distorted proportion arising from hypersecretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1). Although almost never malignant, somatotropinomas may cause significant morbidity and the uncontrolled excess of GH is related to a mortality rate 2 to 4 times higher than expected. Despite the significant efforts made over the last decade, still little is known about the genetic causes of somtotropinomas and even less is applied from this knowledge therapeutically. In this review we attempt to address the genetic and molecular knowledge regarding somatotropinomas and its therapeutic aspects.

**Keywords**: acromegaly, aryl hydrocarbon receptor interacting protein, pituitary tumors, multiple endocrine neoplasia, tumorigenesis

## 4.2 Introduction

The anterior pituitary gland develops from fore gut endoderm with a series of cell lineages arising from precursor cells. The programme of cell commitment and differentiation in the developing pituitary gland arises from the activation of a cascade of transcription factors with ordered temporal patterns of expression. Pit-1 is essential for normal development of somatotrophic, lactotrophic and thyrotrophic cells, and Pit-1 mutations are found in some cases of combined pituitary hormone deficiency. Another transcription factor, Prop-1, has been found to be mutated in several cases of hypopituitarism in which gonadotroph function is also deficient.[53, 54]

Assessments based on unselected populations undergoing autopsy or magnetic resonance imaging (MRI) suggest that pituitary tumors occur very frequently. Metaanalysis conducted by Ezzat et al. found an overall estimated prevalence of pituitary adenomas of 16,7%.[55] Newer epidemiological evidence suggest an overall rate of one case of clinically relevant pituitary adenoma in 1064 of the population.[56] The pituitary tumors belong to family of neoplasms named neuroendocrine tumors (NET). NET originate in endocrine glands (such as the pituitary, parathyroid, or the neuroendocrine adrenal glands), in endocrine islets (within the thyroid or pancreas) as well as in endocrine cells dispersed between exocrine cells throughout the digestive or respiratory tracts.[57] The absence of on-going expansion of the majority of pituitary adenomas and the slow growth

rate of almost all the remainder, their occasional tendency to spontaneously regress or resolve irrespective of size, their sexually dimorphic behavioral phenotypes and generally unremarkable histology, the retention of regulated secretory phenotype in many cases, their trophic response to debulking and the induction of remission after removal of histologically normal pitiuitary tissue, are all characteristics that are somewhat at odds with what might be expected of desregulated growth following the acquisition of genetic defects in oncogenes and tumor supressors.[58]

The pathogenesis of pituitary tumors is still under debate, although a monoclonal origin has been shown. Activating and inactivating mutations may be involved in pituitary tumorigenesis. Regarding inactivating mutations of suppressor genes, they generally follow the Knudson two-hit model in which susceptibility to disease is conveyed by a mutant germ-line allele, and clinically overt disease occurs when the second allele is lost through a somatic mutation, usually as a result of total or partial loss of the chromosome.[59-62] The majority of pituitary adenomas are sporadic, although some arise as a component of familial syndromes. Four genes have been identified that predispose to familial pituitary tumorigenesis. Previously identified, multiple endocrine neoplasia type I (MEN1) (11q13) and protein kinase A regulatory subunit-1-alpha (PRKAR1A) (17q24) genes have been associated in multiple endocrine neoplasia type 1 (MEN1) and Carney Complex (CNC), respectively. More recently identified primary adenoma predisposition (PAP) genes cyclin-dependent kinase inhibitor 1B (CDKN1B) (12p13) and aryl hydrocarbon receptor (AHR) interacting protein (AIP) (11q13) are associated in MEN1-like phenotype and PAP, respectively. In

addition, familial pituitary adenomas is seen in the isolated familial somatotropinomas (IFS) (linkage to 11q13) and familial isolated pituitary adenomas (FIPA).[63, 64]

The scope of this review is to assess the genetic and molecular mechanisms influencing GH-secreting pituitary tumor presentation and its treatment. We will also review the genetic related syndromes associated to these tumors.

### 4.3 Multiple Endocrine Neoplasia Type 1 (MEN1)

MEN-1 syndrome is inherited as an autossomal-dominant trait. The condition is characterized by predisposition to pituitary adenomas, parathyroid hyperplasia, and pancreatic endocrine tumors. MEN (11q13) is one of the first identified tumor suppressor genes.[65, 66]

The MEN 1 gene consists of ten exons that encode the 610-amino acid protein menin. MEN-1 represents a putative tumor suppressor gene and has been localized to chromosome 11q13. Recent studies have shown that menin interacts with a number of proteins that are involved in transcriptional regulation, genome stability, cell division and proliferation.[66] The wild-type protein suppresses the AP-1 transcription factor JunD. JunD is involved in histone deacetylation, inhibits NF-κB activation and interacts with Smad3, which is required for signaling by transforming growth factor-β, nm23 (a putative tumor metastasis suppressor gene), glial fibrillary acidic protein and vimentin, all of

which participate in the cytoplasmatic intermediary filament network and suggest a cytoplasmic action for menin.[61]

Pituitary adenomas occur in approximately 45% of patients (9% somatotroph and >50% prolactinoma) with MEN1. In sporadic pituitary adenomas, MEN 1 gene polymorphisms occur in 30% of cases, loss of heterozygosity on 11q13 in 14%, and inactivating mutations in the coding region of the menin gene in just over 1%.[67] The estimated penetrance of GH producing adenoma in MEN-1 at the age of 40 is about 5%.[68] The frequency of somatotropinomas is much higher in patients with the sporadic type of disease as compared with the familial type. In one large cohort of patients with sporadic MEN-1, somatotropinomas were present only in those patients in whom no germ-line mutation was present. Thus, the relationship of somatotropinomas (as compared with other types of pituitary tumors) to mutations in MEN-1 gene is uncertain.[61] Dreijerink et al described a MEN-1 germ-line mutation in intron 3 (IVS3-6C>G) in a patient and nine members of his family, however none of the relatives had developed any MEN-1 related lesion. Nine percent of MEN-1 patients showed temporary IGF-1 elevations, suggesting that possibly, acromegaly in MEN-1 is preceded by a transient acromegalic state.[69] A germline non-sense mutation (TGG>TAG at codon 76) in the human Cdkn1b gene was identified in a MEN-like condition characterized by acromegaly and primary hyperparathyroidism. Cdkn1b gene encodes the cyclin-dependent kinase inhibitor (CKI) $p27^{Kip1}$.[63] Members of the $p21^{Cip1}$, $p57^{Kip2}$ and $p27^{Kip1}$ cyclin-kinase inhibitor family of proteins inhibit progression from G1 into synthesis (S) phase in the cell cycle.[58] Aaltonen L found p27 germline mutation in one of 26 individuals who had pituitary adenoma

or who clinically tested negative for MEN-1.[70] Igreja S et al. studied 18 sporadic and 3 familial cases of MEN 1 mutation-negative MEN-1 syndrome and they did not found mutations in the coding region or exon/intron junction of the CDKN1B and AIP genes.[71]

### 4.4 McCune-Albright syndrome (MAS)

McCune-Albright syndrome (MAS) is a multigland sporadic syndrome characterized by somatotroph hyperplasia and polyostotic fibrous dysplasia of the bones. MAS is related to the GNAS1 (stimulatory α subunit of G protein) gene mutation.[72]

Heterotrimeric G proteins are membrane-anchored multisubunit enzymes that transduce hormone signals from the cell from the cell-surface-ligand-receptor complexes to downstream effectors. The stimulatory G proteins (Gs) regulate signalling by G-protein-coupled receptors, such as the growth-hormone (GH)-releasing hormone (GHRH) receptor, which regulates GH synthesis and secretion by somatotrophs. Some of the first molecular defects that are associated with endocrine neoplasias were identified in the Gsα subunit. One tumor-associated mutation converts arginine-201 to a cysteine residue, and a second, less-frequent mutation converts glycine-227 to arginine. Substitutions at these codons disrupt GTP hydrolysis, leading to constitutive activation of Gsα and subsequent activation of adenylyl cyclase. These G-protein oncogenes

were first described in a subset of pituitary somatotroph adenomas and in hormone-secreting tumors of other glands, and represent the basis of the McCune-Albright syndrome (MAS).[73, 74] G-protein mutations are frequently detected in the maternal allele, which is consistent with monoallelic imprint of this gene in the pituitary. There is no correlation between G-protein mutations and patient age, gender, tumor size or circulating GH levels.[75] These mutations occur most frequently in somatotrophs,[76] and tumors that carry these mutations are more susceptible to inhibition of GH secretion by somatostatin analogs, such as octreotide.[77] Freda et al screened 60 GH secreting tumors for GNAS mutations. They found that GH secreting tumors harboring GNAS mutations had higher preoperative IGF-1 levels, somewhat higher preoperative GH levels and tended to be smaller than tumors without mutations. Presence of GNAS mutation did not predict a difference in a proliferation marker, surgical remission or response to somatostatin analog therapy.[78]

The family of Rab GTPases coordinates the sequential steps of intracellular transport, such as vesicle formation, motility, and membrane fusion along the secretory pathway. Study by Vasquez-Martinez et al found that somatotropinoma cells are characterized by a high secretory activity concomitantly with a remarkably reduced Rab 18 expression and protein content levels as compared with cells from nonfunctioning pituitary adenoma.[79]

### 4.5 Carney Complex

The complex of “spotty skin” pigmentation, myxomas, endocrine overactivity, and shwannomas” or Carney Complex (CNC) is a multiple endocrine neoplasia (MEN) and lentiginosis syndrome that is inherited in an autossomal dominant manner, and is genetically heterogeneous. Approximately half of the patients with CNC have germline inactivating mutations in the PRKAR1A gene, which codes for the regulatory subunit type 1α of the cAMP-dependent protein kinase A (PKA). GH-producing tumors have been identified so far in several CNC patients with clinically diagnosed acromegaly at the National Institutes of Health. The frequency of PRKAR1A mutations in these patients is the same as in the whole group (approximately 50%).[80] Acromegaly in CNC is characterized by a slow progressive course. The mean age of acromegaly was 35.8 years in the cohort of patients recently reported by Horvath A et al. The disease is slowly developing and fortunately, most often, patients with CNC does not develop an agressive pituitary tumor. A preliminary analysis of a cross between transgenic mice showed that in the presence of a tumorigenic, proliferative signal such as that of GHRH, PRKAR1A deficiency was associated with more significant somatomammotroph hyperplasia.[66] Interestingly, a study by Bertherat et al evaluated 353 patients who carried a germline PRKAR1A mutation or were diagnosed with CNC and/or primary pigmented nodular adrenocortical disease (PPNAD) and found that mutations located in exons were more often associated with acromegaly, myxomas, lentigines and shwannomas.[81]

### 4.6 Isolated Familial Somatotropinoma (IFS)

Isolated Familial Somatotropinoma (IFS), defined as ≥ 2 cases of acromegaly or gigantism in a family in the absence of MEN-1 or CNC, has long been recognized as a clinical entity. IFS is characterized by a slight male predominance and a much younger age at onset (25 years) when compared with sporadic acromegaly, with gigantism being a characteristic feature of IFS kindreds. Tumors in patients with IFS are almost invariably macroadenomas.[61, 64, 82, 83] There have now been additional reports of aryl hydrocarbon receptor interacting protein (AIP) gene mutations in both familial (FIPA and IFS) and sporadic acromegaly. From these recent data, AIP has been suggested to act as a low-penetrance gene in familial pituitary clusters.[84]

AIP contains 6 exons and it encodes a protein of 330 aminoacids. It has a FKBP-homology region in the amino terminus, and three protein-protein interaction mediating tetratricopeptide repeats (TPR) in the C-terminal region. AIP interacts in cytoplasm with the AHR. AHR is a transcription factor that regulates many xenobiotic metabolizing enzymes.[85, 86] Dioxins and dioxin-like chemicals display high affinity binding to AHR, which mediates most of the toxic responses of these agents. Carcinogenic effect of dioxins is likely to result of their tumor promoting activity produced by activation of the AHR. AHR also participates in cellular signaling pathways, e.g. through interaction with known cell-cycle regulators such as retinoblastoma protein.[87] AIP modulates also the sub-cellular localization of AHR and prevents the AHR to undergo nucleocytoplasmic shuttling.[88] Although LOH at 11q13 had been observed by

several groups,[89, 90] the first report to establish a specific region in chromosome 11q13 with linkage to IFS was in 2000.[91] Luccio Camelo et al. in 2004, had narrowed the area involved in the pathogenesis of IFS.[92] In 2005, Soares et al narrowed more the area of the gene involved in the IFS.[93] In 2006, Vierimaa et al identified germline mutations (nonsense mutation Q14X in exon 1, splice site mutation IVS3-1G>A in exon 4 and a nonsense mutation R304X in exon 6) in the AIP gene in individuals with PAP. In a population based series from Nothern Finland, two AIP mutations account for 16% of all patients diagnosed with pituitary adenomas secreting growth hormone and for 40% of the subset of patients who were diagnosed when they were younger than 35 years old.[64] Yu et al examined the frequency of the three AIP mutations in 66 U.S. patients harboring sporadic pituitary tumors and they found no AIP mutations in the patients. A synonymous polymorphism was found in a single patient with acromegaly.[94] Cazabat et al detected AIP mutations in 5 out of 154 patients (3%) patients with apparently sporadic GH secreting tumor in France.[95] Toledo et al. identified a novel germline mutation (Y268X) in AIP gene in four members of a Brazilian family with acromegaly.[84] Naves et al studied 122 subjects of a Brazilian FIPA kindred. Of the ten germline AIP mutation (E174 frameshift) carriers, three had pituitary tumors (two with acromegaly, one with prolactinoma or mixed prolactin/GH secreting tumor), while seven were asymptomatic carriers. The two acromegalic patients had poor response to octreotide.[96] Iwata et al investigated one family with IFS and 40 sporadic GH-secreting adenomas. Germline mutation of AIP (c.286–287delGT on exon 3) was found in the IFS family. In the sporadic adenomas they found no mutations except for a missense mutation (V49M) in a patient with gigantism.[97] A recent cohort of 36

apparently sporadic paediatric pituitary adenoma patients identified a heterozygous in-frame deletion Y248del in one patient.[98] Study by Leontiou C et al evaluated the effects of normal and mutated AIP on cell proliferation and protein-protein interaction in 26 FIPA kindreds and 85 sporadic pituitary adenoma patients. Overexpression of wild-type AIP in TIG3 and HEK293 human fibroblast and GH3 pituitary cell lines dramatically reduced cell proliferation, whereas mutant AIP lost this ability. All the mutations led to a disruption of the protein-protein interaction between AIP and phosphodiesterase-4A5. In normal pituitary, AIP colocalized exclusively with GH and prolactin. In sporadic pituitary adenomas, however, AIP was expressed in all tumor types. In addition, whereas AIP was expressed in the secretory vesicle in GH secreting tumors, similar to normal GH secreting cells, in lactotroph, corticotroph, and non functioning adenomas, it was localized to the cytoplasm but not in the secretory vesicles.[99] Cazabat et al found that patients with AIP mutations resulting in a truncated protein were significantly younger than those bearing a mutation which preserved the structure of the C-terminal end of the protein.[100]

### 4.7 Other molecular alterations in the setting of somatotropinomas

Pituitary tumor transforming gene (PTTG) was originally isolated from rat GH and PRL-secreting cells.[101] Its oncogenic function was proposed on its ability to induce neoplastic transformation of NIH 3T3 cells. PPTG also belongs to the securin family of proteins that control sister chromatide separation during

mitosis.[102] Thus alterations in its expression have been proposed as the mechanism underlying the frequent finding of aneuploidy in human pituitary tumors,[101] although direct evidence for this is lacking. One of the functions of PTTG in facilitating pituitary tumor development appears to be increased angiogenesis.[103]

Lossess in the chromosomal region of the tumor suppressor gene retinoblastoma RB1 (13q14.2) are related to aggressive human pituitary tumor behavior and lack of expression of the protein (pRB) was observed in one fourth of GH-secreting pituitary adenomas.[104] It appears that inactivation of RB1 is critical in human pituitary tumor growth and/or expansion, but not for initial tumor formation.[105]

The epidermal growth factor (EGF) family and its receptors have also been implicated in tumorigenesis in a number of neoplasms. EGF receptor (EGFR) expression correlates with pituitary tumor aggressiveness, mainly for GH producing tumors.[106]

A recent study by Ribeiro-Oliveira Jr. et al evaluated the proteome of human pituitary adenomas and showed the importance of this technique to disclose novel putative proteins in pituitary tumorigenesis. Heat shock protein 110 (HSP110) showed a 33 fold overexpression, the B2 bradykinin receptor a 16 fold overexpression, the C-terminal Src kinase (CSK) protein a 25 fold underexpression and annexin II a 25 fold underexpression in GH-secreting adenomas as compared with normal pituitary tissues. The HPS110 is a

chaperone protein associated with protein folding and its overexpression has been recently described as important in a series of human cancers. The B2 bradykinin receptor is a member of the Kallikrein system, a subgroup of the serine protease family of enzymes, and the importance of its up-regulation in other human cancers has also been described. CSK is a non-receptor protein tyrosin-kinase, its major function being to specifically phosphorylate a conserved C-terminal tyrosine of Src family Kinases. As a consequence of down-regulation of the Src-kinase protein expression and presumably its activity, proto-oncogenic enzymes controlling cell growth and proliferation would diminish. As a calcium-dependent phospholipids-binding protein, annexin II has been suggested to play a role in exocytosis from anterior pituitary secretory cells.[107]

### 4.8 Treatment Aspects

Surgery currently is the preferred approach for treating most patients. Serum GH levels are controlled within an hour after complete removal of the GH-secreting adenomas. Transsphenoidal microsurgical adenomectomy approach is used most commonly and, in the hands of experienced neurosurgeons, cures the majority of patients who are harboring a well-circumscribed microadenoma with serum GH levels less than 40 µg/L. In general, 80% of patients who have microadenoma and approximately 50% of those who have a macroadenoma normalize IGF-1 levels after transsphenoidal adenomectomy.[9] Therefore, as surgery alone is frequently not curative, further treatment is often required.

Currently, there are three drug classes available for the treatment of acromegaly: dopamine agonists (DAs), somatostatin receptor ligands (SRLs), and a GH receptor antagonist (GHRA).

### 4.9 Somatostatin receptor ligands (SRLs)

Somatostatin (somatotrophin release-inhibiting hormone, SST) binds with high affinity to five different subtypes of specific SST receptors (SSTRs) on the cell surface, which belong to the G-protein-coupled receptor family ($SSTR_1$, $SSTR_2$, $SSTR_3$, $SSTR_4$, $SSTR_5$).[108, 109] All five SSTRs bind to the natural SST, while its synthetic analogues have a limited affinity, binding mainly to $SSTR_2$, and much less to $SSTR_5$. The five receptors share common signalling pathways such as the inhibition of adenyl cyclase, activation of phosphotyrosine phosphatase or modulation of mitogen-activated protein kinase (MAPK) through G-protein-dependent mechanisms.[110]

The SRLs signal predominantly via somatostatin receptors subtypes 2 and 5, leading to a decrease in adenoma GH secretion. The use of SRLs is most appropriate as first-line therapy when there is a low probability of a surgical cure (for example, large extrasellar tumors with no evidence of central compressive effects), after surgery has failed to achieve biochemical control, before surgery to improve severe comorbidities that prevent or could complicate immediate surgery (the benefits of it are unproven), to provide disease control or partial control and in the time between administration of radiation therapy and the

onset of maximum benefit attained from radiation therapy (radiation therapy can take several years to produce disease control).

In unselected populations, SRLs reduce GH to < 2,5 ng/mL and normalize IGF-1 in 44 and 34% of patients, respectively. Tumor shrinkage of > 20% occurs in approximately 75% of acromegaly patients receiving these drugs (mean 50% reduction in tumor volume).[111]

Due to the limited affinity of the synthetic analogues, new SST analogues (SSA) were studied and developed: pasireotide (SOM 230, Novartis) is a new "universal" or "pan-receptor" SSA, having a high affinity for $SSTR_1$, $SSTR_2$, $SSTR_3$ and $SSTR_5$ subtypes.[112] Its receptor-binding profile is 30-40 times higher for SSTR1 and SSTR5 than for octreotide, which is a somatostatin analogue available for clinical use with high binding affinity for SSTR2, less affinity for subtype 5 and lowest affinity for subtype 3.[113-116] SST and its analogues were demonstrated to have direct anti-proliferative effects in a variety of tumor cells by inhibiting the mitogenic signalling of growth factor receptor kinases, but also by inducing apoptosis.[109, 117, 118] They also inhibit the secretion of IGF-1, which has been thought to be involved in the recurrence, growth and aggressiveness of some endocrine and non endocrine tumors.[119]

Thodou et al studied the expression of $SSTR_1$, $SSTR_{2A}$, $SSTR_{2B}$, $SSTR_3$, $SSTR_4$ and $SSTR_5$ in tissues microarrays of 90 pituitary adenomas. In somatotroph adenomas, $SSTR_5$ and $SSTR_{2A}$ predominated. They found that

$SSTR_{2B}$ was expressed in the great majority of somatotroph adenomas, however, the level of expression was considerably less than for $SSTR_{2A.}$[120]

The relationship between SSTR expression and their functionality may be more complex in GH-secreting adenomas expressing low levels of $SSTR_2$, where the $SSTR_2$ –preferential ligand octreotide is ineffective in suppressing GH release. In such cases, an $SSTR_5$ selective agonist may be of value because this SSR subtype is often highly expressed.[121] However, in this specific settting, a bi-specific analogue, such as BIM-2344, which can active both receptors, could achieve a better control of GH hypersecretion.[121] Moreover, a selective $SSTR_1$ ligand, BIM-23926, has been shown to inhibit in vitro hormone secretion and cell viability in GH- and PRL-secreting adenomas in a subset of non-functioning pituitary adenomas (NFPAs).[122, 123] Moreover, SSTR act not just as monomers but may display a differential tendency to homo- and heterodimerise, depending on the subtype involved, and perhaps also on the cell type in which they are expressed.[124]

There is a general agreement that patients harbouring tumors with mutations of the Gsα gene that constitutively activate adenylyl cyclase are highly sensitive to the inhibitory action of somatostatin. Conversely, because no mutations of SST2 and SST5 genes are usually found in resistant patients, resistance to somatostatin has been attributed to a reduced expression of SST2 e SST5. To date, a mutational change involving a somatostatin receptor was the germline R240W mutation in the SSTR5 gene in one acromegalic patient resistant to octreotide. Recently, LOH at the SST5 gene locus (located at chromosome

16p13.3) has been evaluated in a series of somatotroph and thyrotroph adenomas[125] taking advantage of the Pro335Leu substitution (C1004T) that is a common polymorphism previously reported in the Danish and British populations. By this approach, 2 tumors (1 somatotroph and 1 thyrotroph adenoma) had LOH at the SST5 locus, while 11 retained the 2 alleles.[126] Filopanti et al also found that patients with SSTR5 c1004 allele (P335) showed IGF-I levels significantly lower than patients homozygous for 1004t (335L). Moreover, serum GH levels were lower in patients having c1004 allele and no t-461 allele.[127] Taboada et al. showed that somatostatin receptor subtype 2 mRNA expression levels correlate positively with in vivo hormonal and tumor volume responses to octreotide LAR.[128]. Despite the fact that most studies suggest that *gsp*-positive adenomas respond better to octreotide LAR compared to *gsp*-negative tumors, a recent study failed to find differences in octreotide LAR sensitivity according to *gsp* gene status.[129]

Recently, the analysis of the first randomized, double-blind, placebo-.controlled, multicenter, phase IIIb study of octreotide LAR in patients with metastatic NETs of the midgut showed that octreotide LAR significantly lengthens median time to tumor progression compared with placebo.[130]

The mode of action of the somatostatin analog octreotide on neuro-endocrine tumor proliferation is largely unknown. Overexpression of the proto-oncogene Akt/PKB (protein kinase B) has been demonstrated in certain neuro-endocrine tumors. Akt activates downstream proteins including mTOR and p70S6K, which play an important role in cell proliferation. RAD001 (everolimus) is a novel agent

that is being trialled in the treatment of neuro-endocrine tumors, as is known to interact with mTOR. Study by Grozinsky-Glasberg S et al found that the treatment of rat insulinoma cell line with octreotide and RAD001 inhibited proliferation and attenuated phosphorylation of all downstream targets of Akt: TSC2, mTOR, and p70S6K.[131]

### 4.10 Dopamine agonists (DAs)

Dopamine receptors belong to the family of seven transmembrane domain G protein coupled receptors and include five different receptor subtypes, named D1-D5. The analysis of dopamine receptor structure and function suggests the existence of two different groups of receptors: D1-like, including D1 and D5 receptors, generally associated to a stimulatory function, and D2-like, including D2-D4 receptors, generally associated to an inhibitory function. The D2 receptor exists in two main variants, the long isoform named D2L and the short isoform named D2S. Dopamine binds all five receptors although among the D1-like receptors it binds the D1 with lower affinity than the D5 receptor, and among the D2-like the D2 with lower affinity than D3 and D4 receptors. Beyond dopamine, bromocriptine preferentially binds D2-like receptors but is able to bind to D1-like receptors as well. Cabergoline is able like bromocriptine to bind both D1 and D2 receptors, with higher affinities for both receptors and higher selectivity for D2 receptors. Moreover, cabergoline has recently been demonstrated to possess a higher affinity than bromocriptine not only for both D2 receptor isoforms, but also for D3 and D4 receptors. Recently, both D2S and D2L receptor isoforms

have been demonstrated to activate, through the involvement of Gβγ subunits and protein kinase C, the mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) pathway, generally involved in the regulation of cell growth, differentiation and apoptosis. In particular, in pituitary tumor cell lines, dopamine agonists have found to exert a clear anti-proliferative effect.[132] Indeed, the dopaminergic agents have been the mainstay in the treatment of prolactinomas. Futhermore, somatotroph pituitary tumors occasionally show dramatic anti-secretory and anti-proliferative responses to dopaminergic agents.[133] Study by Zatelli et al suggested that adenomas expressing D2 are less likely to respond to SRL analogues in terms of inhibition of GH secretion.[134] Moreover, knowing the association of SSRs and D2 receptor in the majority of pituitary adenomas, another chemical approach consisted in the synthesis of chimeric molecules containing structural elements of both somatostatin and DA directed against both the superfamilies of G-protein-coupled receptors (GPCRs).[135-137] The first molecules of this class, BIM-23A387 and BIM-23A760, were characterised by their SST2 and D2 and SSTR2, SST5 and D2 affinity respectively, and resulted effective in controlling hormone hypersecretion in vitro in somatotroph adenomas that there partial responders to octreotide.[138]

Bromocriptine and cabergoline have been used as adjuvant therapy for acromegaly. Bromocriptine suppresses serum GH level to less than 5 μg/L in less than 15% of patients who have acromegaly when used in high doses (up to 20 mg per day), and patients report reduced soft tissue swelling, perspiration, fatigue, and headache. Cabergoline is a long-acting dopamine agonist that

reduced serum GH levels than 2 µg/L and normalized IGF-1 in approximately 30% of patients. In light of recent studies demonstrating increased incidence of valvular heart disease with high doses of cabergoline, this mode of treatment should be undertaken with caution.[9] Clinical situations in which cabergoline may be useful include when the patient prefers oral medication (DAs are the only oral medication available for acromegaly); after surgery (very occasionally as first line therapy) in selected patients, such as those with markedly elevated prolactin and/or modestly elevated GH and IGF-1 levels and as additive therapy to SRL therapy in patients partially responsive to a maximum SRL dose – approximately 50% of such patients may achieve control of GH and IGF-1 levels with combination therapy.[111]

Recent study by Grossrubatscher et al evaluated 46 NET samples and found that 85% of samples (100% of bronchial carcinoids and 93% of islet cell tumors) showed positivity for D2R, demonstrating the potential role of dopaminergic drugs in inhibiting secretion or cell proliferation in NETs.[139]

### 4.11 **Growth hormone antagonist (GHRA)**

GH regulates somatic growth, substrate metabolism and body composition. Its actions are elaborated through the GH receptor (GHR), a member of the cytokine superfamily that includes receptors for prolactin, erythropoetin, leptin, and the interleukins. Dimerization of GHR is an initial and crucial event in GH signalling. GHR is a four helix bundle with an unusual topology and GH binding

to GHR monomers was thought to be sequential. The initial step of GH binding to its receptor involves high-affinity binding to site 1 to one GHR monomer followed by lower affinity binding of site 2 to a second GHR monomer. Recent studies indicate that GHRs exist as a pre-formed dimmer. A conformational change in the extracellular domain of the GHR is triggered by GH binding which initiates signalling. Janus Kinase (JAK) activation is triggered by GH binding which induces conformational change of the GHR resulting in JAK transphosphorylation and catalytic activation. The phosphorylation of the receptor results in the activation of a number of signalling pathways. The JAK-STAT pathway is a major effector of GHR signalling, and necessary for the transcriptional regulation of IGF-1. The mitogen activated protein kinase (MAPK) pathway, and the phosphatidylinositol 3'-kinase (PI3K) pathway are also activated by JAK2 transphosphorylation. The termination of GH signalling is an important mechanism for controlling GH action. This is controlled by two systems, the suppressors of cytokine signalling (SOCS) proteins and the protein tyrosine phophatases (PTPs). GH induces the expression of SOCS-1, SOCS-2, and SOCS-3, which feedback to inhibit transcriptional action. Among the PTPs, SHP1 and SHP2 inactivate the receptor by dephosphorylating JAK2.[140] Gly-119 in bovine GH, which corresponds to Gly-120 in hGH, is invariant in the amino acid sequences of GH family members, suggesting that this residue is crucial for the functioning of GH. Mutational studies showed that replacing this Gly with several amino acids other than Ala resulted in a hGH antagonist. A subsequent report confirmed that replacing hGH G120 with arginine resulted in GH antagonist. Like wild-type hGH, genetically engineered variants of GH are rapidly cleared by the kidney and have very short elimination half-lives. To

overcome these problems, the GH antagonist (hGH G120R) was then pegylated. In addition to the single amino acid modification of binding site 2 (G120R), the pegvisomant molecule has modifications at the binding site 1 that increase binding affinity and give it competitive binding advantage over wild-type hGH. The eight substitutions in binding site 1 are H18D, H21N, R167N, K168A, D171S, K172R, E174S, I179T. It has recently been suggested that the crucial changes are K168A and K172R, both Lys residues.[141] Sensitivity to pegvisomant therapy is highly variable in patients with acromegaly but determinants of this variability are still unknown. Lack of exon 3 (d3-) of the Growth hormone receptor has been associated with increased biological activity of GH. Bianchi A et al determined the GH receptor genotype from nineteen acromegalic patients and found that d3-GHR patients required a significant lower dose of pegvisomant and shorter treatment time to normalize IGF-1.[142]

The indications for Growth hormone antagonist (GHRA) include patients that have persistently elevated IGF-1 levels despite maximal therapy with other treatment modalities, possibly as monotherapy or in combination with a SRL in other patients. However more data are required before firm guidelines can be given on this.[111]

Sensitivity to Pegvisomant is highly variable in acromegaly; in fact, normalization of serum IGF-1 levels, which is obtained in up to 97% of patients, may require damatically variable amount of drug (from 10 mg to 80 mg/daily).[142]

## 4.12 Conclusions

Pituitary adenomas comprises nearly 15% of intracranial neoplasms[143] and Acromegaly is associated with an increase in mortality, specially related to its cardiovascular complications and many patients still cannot be cured with the treatment options available. A number of genetic factors act in the process of pituitary tumorigenesis and the understanding of the molecular and genetic phenomena involved in this disease is crucial for the development of new diagnostic and therapeutic tools. New discoveries have been made specially regarding the mechanisms involved in resistance to treatment and new chimeric compounds. Despite significant progress has been made in understanding the molecular basis of this pituitary tumorigenesis, the mechanisms that lead to selection of the abnormal proteins during pituitary tumorigenesis are largely unknown. Widespread genetic screening for the known mutations requires careful consideration since there is divergence in the penetrance of pituitary adenomas. More efforts must be made towards better correlation between molecular and clinical aspects of acromegaly.

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## 4.14 List of Abbreviations

GH – growth hormone

IGF-1 – insulin-like growth factor 1

Pit-1 – pituitary-specific transcription factor 1

Prop-1- paired-like homeodomain transcription factor

MRI – magnetic resonance imaging

MEN-1 – multiple endocrine neoplasia type 1

PRKAR1A – protein kinase A regulatory subunit-1-alpha

CNC – Carney complex

PAP – primary adenoma predisposition

CDKN1B – cyclin-dependent kinase inhibitor 1B

AHR – aryl hydrocarbon receptor

AIP - aryl hydrocarbon receptor interacting protein

IFS – isolated familial somatotropinomas

FIPA – familial isolated pituitary adenomas

AP-1 – activator protein 1

NF-κB - nuclear factor kappa-light-chain-enhancer of activated B cells

Smad3 - mothers against decapentaplegic homolog 3

nm23 – nonmetastatic gene 23

MAS - McCune-Albright syndrome

Gs – stimulatory G protein

GHRH – growth-hormone releasing hormone

Gsα – stimulatory G protein α subunit

GTP - guanosine-5'-triphosphate

GNAS - adenylate cyclase-stimulating G alpha protein gene

TPR – tetratricopeptide repeats

PPTG – pituitary tumor transforming gene

PRL – prolactin

RB-1 – retinoblastoma 1

pRB – retinoblastoma protein

EGF – epidermal growth factor

EGFR - epidermal growth factor receptor

cAMP – cyclic adenosine monophosphate

HPS 110 – heat shock protein 110

CSK – C-terminal Src kinase

DAs – dopamine agonists

SRLs – somatostatin receptor ligands

GHRA – growth hormone receptor antagonist

SST – somatostatin

SSTRs – somatostatin receptors

MAPK – mitogen-activated protein kinase

SSA – somatostatin analogs

NFPAs – non-functioning pituitary adenomas

LOH – loss of heterozygosity

mRNA - messenger ribonucleic acid

LAR – long acting release

*g*sp - stimulatory G protein α subunit protein

ERK – extracellular signal-regulated kinase

GHR – growth hormone receptor

GHRA – growth hormone receptor antagonist

JAK – janus kinase

PI3K – phosphatidylinositol 3´-kinase

SOCS – supressors of cytokine signalling

PTPs – protein tyrosine phosphatases

SHP - Src homology region 2 (SH2) domain-containing phosphatase

hGH – human growth hormone

Gly - glycine

## 4.15 Tables and Figures

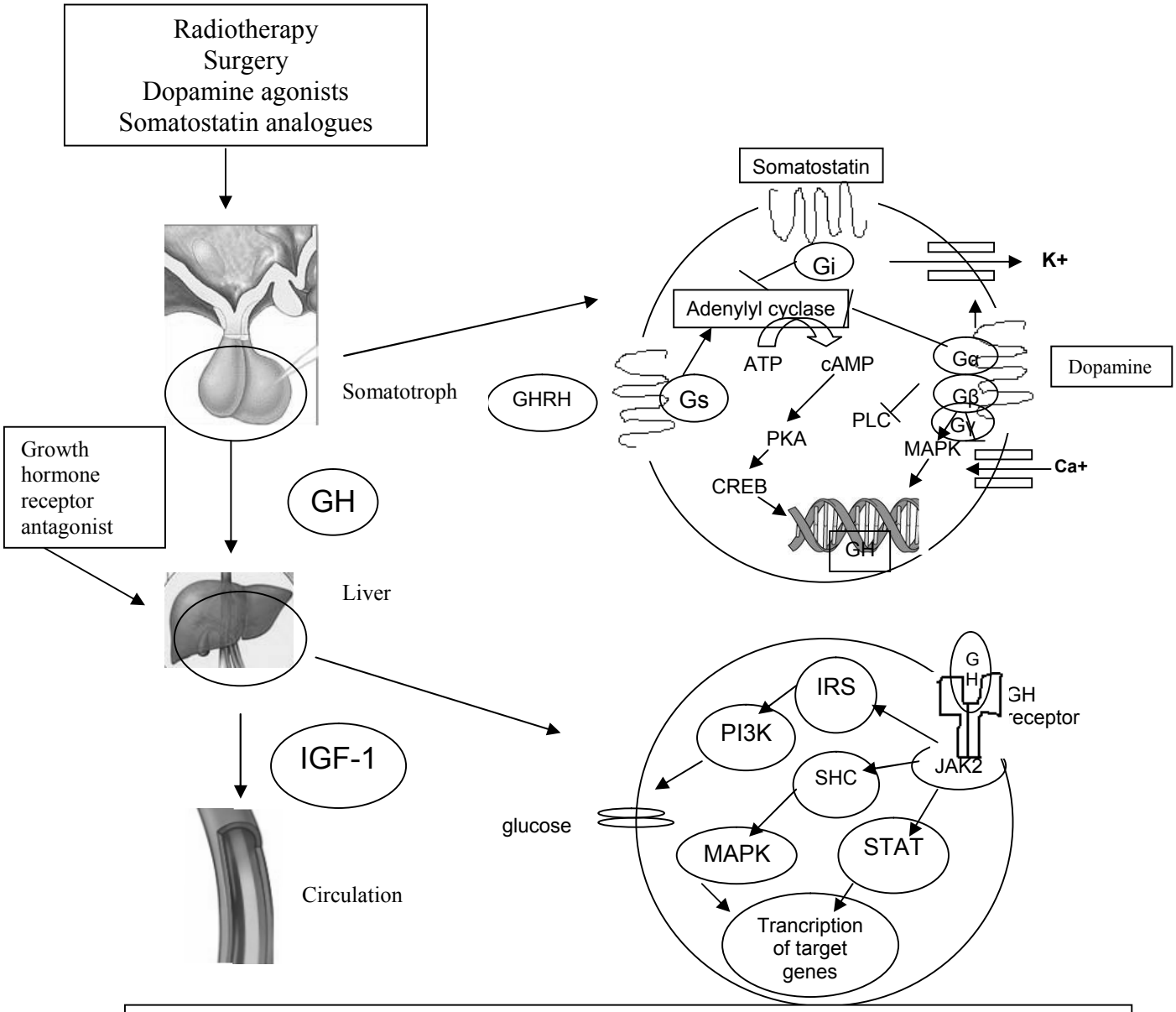


**Fig 1 Regulatory pathways in somatotrophic and peripheral cells.**
The somatotroph expresses cell-surface receptors for growth hormone-releasing hormone (GHRH) – a seven transmembrane domain G-protein-coupled receptor. Ligand binding induces conformational changes that result in dissociation of the α-subunit from the β- and γ-subunits of the stimulatory G protein (Gs), which activates adenylyl cyclase to generate cyclic AMP from ATP. The cAMP, in turn, activates intracellular protein kinases, including protein kinase A (PKA), which phosphorylates and activates nuclear localization of CREB. In the nucleus, CREB activates transcription factors that activate the growth hormone (GH) gene, which promotes proliferation. GH synthesis and secretion are inhibited by somatostatin, which signals through its G-protein-coupled receptor to activate the inhibitory Gi protein. Gi signalling leads to reduced intracellular calcium levels and inhibition of adenylyl cyclase. Dopamine and cabergoline bind to D2-like receptors, which are seven-transmenbrane domain G-protein-coupled receptor, and signal through Gi protein. In peripheral cells, GH binding to the GH receptor (GHR) induces conformational change of the GHR, which activates JAK2. The phosphorylated JAK2 initiates a multitude of signalling pathways as JAK/STAT, PI3K/AKT and MAPK pathways. Among them JAK/STAT pathway is critical for a variety of GH functions and necessary for the transcriptional regulation of IGF-1. The GHR-JAK2 activation of signalling molecules can result in different cellular responses, some of which involve the activation of transcription from target genes, while others involve metabolic changes like the activation of IRS which results in the induction of the insulin-like action of GH.

A acromegalia é uma doença associada à mortalidade aumentada, principalmente devido a causas cardiovasculares. É reconhecida a frequência elevada de fatores de risco cardiovascular como hipertensão arterial, dislipidemia e diabetes mellitus nos pecientes acromegálicos e o controle da doença é capaz de reduzir a elevada taxa de mortalidade dessa população. O controle da doença ainda é difícil com o atual arsenal terapêutico e vários avanços genéticos e moleculares tem sido obtidos com o intuito de aumentar a compreensão dos mecanismos de apresentação da acromegalia e da resposta ao seu tratamento.

Diante desses fatos, o objetivo dessa tese na forma de dois artigos foi avaliar a frequência de fatores de risco cardiovascular e síndrome metabolica em pacientes com doença controlada e descontrolada; e também rever os recentes avanços genéticos e moleculares que envolvem a doença.

No primeiro artigo, apesar da elevada frequência encontrada dos fatores de risco cardiovascular nos pacientes com acromegalia, não conseguimos achar diferença nessa frequência entre o grupo de pacientes com doença descontrolada e controlada. Após análise multivariada, o GH e o IGF-1 se correlacionaram inversamente com o colesterol LDL ($p = 0.012$ e $p = 0.006$ respectivamente) e o HOMA IR se correlacionou diretamente com o IGF-1 ($p = 0.018$). GH também mostrou correlação inversa com a circunferência abdominal (OR = 9.6, CI = 1.1 – 87.1, $p = 0.044$), o que era esperado diante dos efeitos lipolíticos reconhecidos do GH. No nosso grupo de pacientes, o

sexo feminino se correlacionou com níveis mais altos de colesterol total e LDL colesterol. Uma possível razão para esse achado, seria o fato da maior parte das pacientes estar na faixa etária da menopausa e não estar fazendo reposição estrogênica. Observamos que os pontos de corte de GH de 1, 2.0 e 2.5µg/L, apresentam baixa sensibilidade em detectar a presença de fatores de risco nesses pacientes. Pontos de corte de GH extremamente baixos (entre 0.07 e 0.38 µg/L) apresentam sensiblidade de 90% para detecção desses fatores de risco.

O segundo artigo revê as mutações genéticas envolvidas nas formas familiares e não familiares de acromegalia, além de alterações em nível de receptor e pós receptor que influenciam o tratamento da doença. São também levantados os desafios no avanço da pesquisa nessa doença.

## 6. Apêndices

Tabela 9. Critérios diagnósticos do NCEP/ ATP III para Síndrome Metabólica, 2001

| |
|---|
| 1. Obesidade abdominal: Cintura > 102 cm em homens e 88 cm em mulheres |
| 2. Níveis de triglicerídeos > 150 mg/dL |
| 3. Colesterol HDL < 40 mg/dL em homens e < 50 mg/dL em mulheres |
| 4. Pressão arterial ≥ 130/85 mmHg |
| 5. Glicemia jejum ≥ 110 |
| Presença de 3 ou mais critérios acima |

Tabela 10. Critérios diagnósticos da OMS para Síndrome Metabólica, 1999

| |
|---|
| 1. Pressão arterial elevada ≥ 160/90 mmHg |
| 2. Hiperlipidemia: triglicerídeos ≥ 150 mg/dL e/ou colesterol HDL < 35 mg/dL em homens e < 39 mg/dL em mulheres |
| 3. Obesidade central: relação cintura/quadril > 0,90 em homens e > 0,85 em mulheres e/ou IMC < 30 $Kg/m^2$ |
| 4. Microalbuminúria: excreção urinária de albumina ≥ 20 µg/min |
| Presença de diabetes mellitus, intolerância à glicose ou resistência insulínica, associadas a dois ou mais dos critérios acima |

Tabela 11. Critérios diagnósticos da IDF para Síndrome Metabólica, 2005

| |
|---|
| 1. Níveis de triglicerídeos ≥ 150 mg/dL |
| 2. Colesterol HDL < 40 mg/dL em mulheres e < 35 mg/dL em homens |
| 3. Pressão arterial ≥ 130/85 mg/dL |
| 4. Glicemia jejum > 100 mg/dL |
| Presença de obesidade central mais dois ou mais critérios acima |

Tabela 11.1 Critérios de Obesidade central da IDF de acordo com origem étnica

| Origem étnica | Homens | Mulheres |
|---|---|---|
| Európides | 94 cm | 80 cm |
| Sudeste asiático | 90 cm | 80 cm |
| Chineses | 90 cm | 80 cm |
| Japoneses | 85 cm | 90 cm |

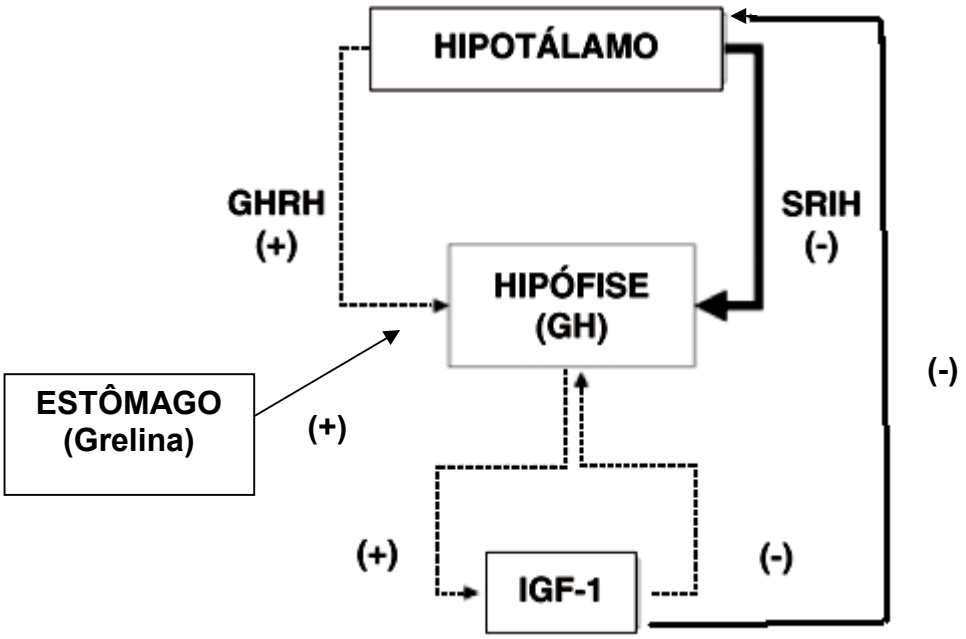


**Fig 2. Controle da Secreção de GH**
O hipotálamo produz o hormônio liberador de GH (GHRH), principal estimulador da secreção de GH na hipófise. O hipotálamo também produz somatostatina (SRIH), a qual exerce um efeito inibidor sobre a produção de GH na hipófise. Já a grelina produzida pelo estômago estimula a secreção de GH. O GH produzido irá se ligar ao seus receptors nas células e fígado. Neste último, ele estimula a síntese do fator de crescimento insulina-símile IGF-1. O IGF-1 livre se liga aos seus receptors nas diversas células induzindo crescimento e proliferação. No hipotálamo e hipófise, o IGF-1 exerce feedback negativo sobre a produção de GHRH e GH respectivamente.