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Plasma insulin-like growth factor-II (IGF-II) and IGF-II/IGF-I ratio in a chilean case of Doege-Potter Syndrome

HUGO E. TOBAR*, PhD.[1], RODRIGO IBACETA*, MD.[1], ANA-MARÍA FIGUEROA, PhD.[1], VERÓNICA QUIÑONES, BQ.[1], GERMÁN IÑIGUEZ, MSc.[2], PATRICIO SALMAN, MD.[3], VALENTINA SERRANO, MD.[1], LORENA SALINAS, MD.[1], JOSÉ LUIS SANTOS, PhD.[1]

[1]Departamento de Nutrición, Diabetes y Metabolismo, Escuela de Medicina, Pontificia Universidad Católica de Chile. Santiago, Chile.
[2]Instituto de Investigaciones Materno Infantil (IDIMI), Facultad de Medicina, Universidad de Chile. Santiago, Chile.
[3]Sección Endocrinología y Diabetes, Departamento de Medicina Interna, Universidad de Concepción. Concepción, Chile.

*Contributed equally to this report.

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Corresponding Author:
José L. Santos.
Departamento de Nutrición, Diabetes y Metabolismo, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
jsantosm@uc.cl

Introduction: *Doege-Potter syndrome is a rare clinical entity characterized by recurrent hypoglycemic events caused by non-pancreatic tumors secreting an incompletely processed high-molecular-weight form of Insulin-like Growth factor-II (IGF-II).* ***Aim:*** *To report IGF-II and IGF-I circulating levels in a Chilean case of Doege-Potter syndrome and control individuals, and to identify the high-molecular-weight form of IGF-II.* ***Methods:*** *We measured IGF-II and IGF-I plasma levels using enzyme-linked immunoassays (ELISA) in the patient and ten controls. We identified the high-molecular-weight form of IGF-II performed by Western blot.* ***Results:*** *The plasma concentration of IGF-II in the patient was 868.9 ng/mL, which is only slightly > 80th percentile of controls (681,4 ± 212,8 ng/mL; mean ± standard deviation). In contrast, IGF-I plasma concentration in the patient was 17.6 ng/mL, which is notoriously lower than the corresponding levels in controls (109.1 ± 19.1 ng/mL). The IGF-II/IGF-I ratio in the patient was 49.4 (normal value < 10), which is 7.8 times higher compared to the average ratio of controls (6.3 ± 1.5). The high-molecular form of IGF-II presence in samples was confirmed through Western blot.* ***Conclusions:*** *The plasma IGF-II/IGF-I ratio better indicates the Doege-Potter syndrome's metabolic impairment than isolated measurements of circulating IGF-II or IGF-I levels.*

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Key words: *Hypoglycemia; Insulin-Like Growth Factor I; Receptor, IGF Type 2; Solitary Fibrous Tumor, Pleural.*

Factor de crecimiento similar a la insulina-II (IGF-II) y razón IGF-II/IGF-I en un caso chileno de síndrome de Doege-Potter

Introducción: *El síndrome de Doege-Potter es una rara entidad clínica caracterizada por eventos hipoglicémicos recurrentes causados por tumores no-pancreáticos que secretan una forma incompletamente procesada con alto peso molecular del factor de crecimiento similar a la insulina-II (IGF-II).* ***Objetivo:*** *Reportar los niveles circulantes de IGF-II e IGF-I en un caso chileno de síndrome de Doege-Potter y en controles, así como identificar la forma de alto peso molecular de IGF-II.* ***Métodos:*** *Los niveles plasmáticos de IGF-II e IGF-I se determinaron mediante inmunoensayos de tipo ELISA en el caso índice y en 10 controles. La forma de alto peso molecular de IGF-II se identificó mediante western-blot.* ***Resultados:*** *La concentración plasmática de IGF-II en*

el paciente fue de 868,9 ng/mL, que es sólo ligeramente superior al percentil 80 del grupo control (681,4 ± 212,8 ng/mL; media ± desviación estándar). Sin embargo, la concentración plasmática de IGF-I en el paciente fue de 17,6 ng/mL, que es notoriamente inferior a la de los controles (109,1 ± 19,1 ng/mL). La razón IGF-II/IGF-I en el paciente fue de 49,4 (valor normal < 10), que es 7,8 veces superior a la media de los controles (6,3 ± 1,5). La presencia de la forma de alto peso molecular de IGF-II se confirmó mediante western-blot. ***Conclusiones:*** *La razón IGF-II/IGF-I en plasma es un mejor indicador de las alteraciones metabólicas del síndrome de Doege-Potter que las mediciones aisladas de IGF-II o IGF-I circulantes.*

Palabras clave: *Factor I del Crecimiento Similar a la Insulina; Hipoglicemia; Receptor IGF Tipo 2; Tumor Fibroso Solitario Pleural.*

Hypoglycemia is a medical emergency relatively common in the setting of the treatment of glucose lowering agents. However, when it is presented spontaneously and recurrently in severe events, it becomes a diagnostic challenge. A possible cause of such hypoglycemic events is related to mesenchymal tumors outside pancreatic islets[1], such as solitary fibrous tumors (SFT), that occurs most commonly in the pleura[1,2]. Hypoglycemia secondary to SFT has been referred as the Doege-Potter Syndrome[2-4]. The underlying mechanism of hypoglycemia involves the overexpression of immature high-molecular weight forms of Insulin-Like Growth Factor-II (IGF-II), named "Big IGF-II"[5-7]. In the Doege-Potter syndrome, the presence of "Big IGF-II" leads to moderate-high plasma concentrations of IGF-II and a reduction of IGF-I levels[8].

Several clinical cases of Doege-Potter syndrome have been published in Chile[9-13]. However, IGF-II plasma characterization is lacking given that IGFs measurements are not readily available in the clinical context. The aim of this study was to report plasma levels of IGF-II, IGF-I, and IGF-II/IGF-I ratios in a Chilean case of Doege-Potter syndrome[13], as well as to identify high-molecular weight forms of IGF-II.

Subjects and Methods

Case report

A 49-years-old male patient without history of diabetes with a Solitary Fibrous Tumor (SFT) in omentum found at the age of 34 years-old[13]. The patient has a history of multiple resection surgeries due to tumor recurrences, including a splenectomy along with hepatic tumor resection from left lobe as well as intestinal resections due to solitary abdominal fibrous tumors. The patient evolved with recurrent symptomatic hypoglycemia episodes, chemotherapy and cytoreductive surgery. Hypoglycemia was managed with glucose solutions, free consumption of carbohydrates and prednisone. At the time of the biochemical evaluation, measurement in a fasting blood sample of plasma insulin was 9,2 μU/ml and c-peptide<0.1 ng/mL. Plasma levels of IGF-I and IGF-II were measured in the proband and in 10 male adult controls (age range: 25-45 years). This study was approved by Ethics Committee of Pontificia Universidad Católica de Chile.

Plasma IGF-I and IGF-II

Plasma levels of IGF-II and IGF-I were measured using enzyme-linked immunoassays (ELISA R&D Quantikine kits DG100/DG200; https://www.rndsystems.com/) applying a protocol for separation IGFs from their IGF binding proteins (IGFBPs). The presence of high molecular weight forms of IGF-II was detected in plasma by Western Blot using a polyclonal anti-IGF-II antibody (R&D System, cat#AF-292-NA) and a secondary antibody Anti-goat IgG-HRP, (Santa Cruz, cat#SC-2020).

Results

Plasma concentrations of IGF-II in the patient was 868.9 ng/mL, only slightly above the average

value found in controls (681,4 ± 212,8 ng/mL; mean ± standard deviation; 95% reference range: 333-967 ng/mL). In contrast, IGF-I plasma concentration in the patient was 17.6 ng/mL, which is notoriously lower than values found in controls (109.1 ± 19.1 ng/mL, 95% reference range: 98-182 ng/mL) (Figures 1A and 1B). The ratio of circulating concentrations of IGF-II/IGF-I in the patient was 49.4, which is 7.8 times higher compared to the average in controls, and 28.7 standard deviations above their average (6.3 ± 1.5; 95% reference range: 3.3-9.3) (Figure 1C). Normal values of this ratio in the literature are reported to be <10. Western blots in the plasma of the proband and a control identified the presence of high molecular weight forms of IGF-II ("Big IGF-II") (Figure 2A).

Discussion

Doege-Potter syndrome is a rare clinical entity characterized by recurrent hypoglycemic events caused by rare non-islet pancreatic tumors[14]. Increased plasma concentrations of IGF-II and the presence of the "Big IGF-II" are considered as the cause of hypoglycemia[6-8-15]. Plasma IGF-II patient concentration was only slightly above the 80th percentile of controls, probably because blood sampling was drawn after tumor resections and after chemo- and corticotherapy[5,6]. In contrast, IGF-I plasma levels were very low compared to the controls and outside the normal range, leading to a very high plasma IGF-II/IGF-I ratio. Although diffusely, western-blot in plasma indicated the presence of the big IGF-II, thus confirming the key biochemical features of Doege-Potter syndrome.

Apart from its recognized role in growth during fetal and embryonic development, it is proposed that IGF-II overexpression is also linked to tumor development and resistance to chemotherapy, possibly through autocrine mechanisms[15]. It has been also proposed that IGF-II is a relevant and neglected metabolic regulator of glucose homeostasis[16]. The human IGF-II protein (encoded by the IGF2 gene; 10 exons, 5 promoters) is synthesized as a 180-amino acid pre-propeptide containing a 24-amino acid signal peptide at the N-terminal and an additional 89 amino acid extension at C-terminal[17]. Interestingly, the 67-amino acid IGF-II mature protein (~7.5 kDa) shares ~47% amino acid homology

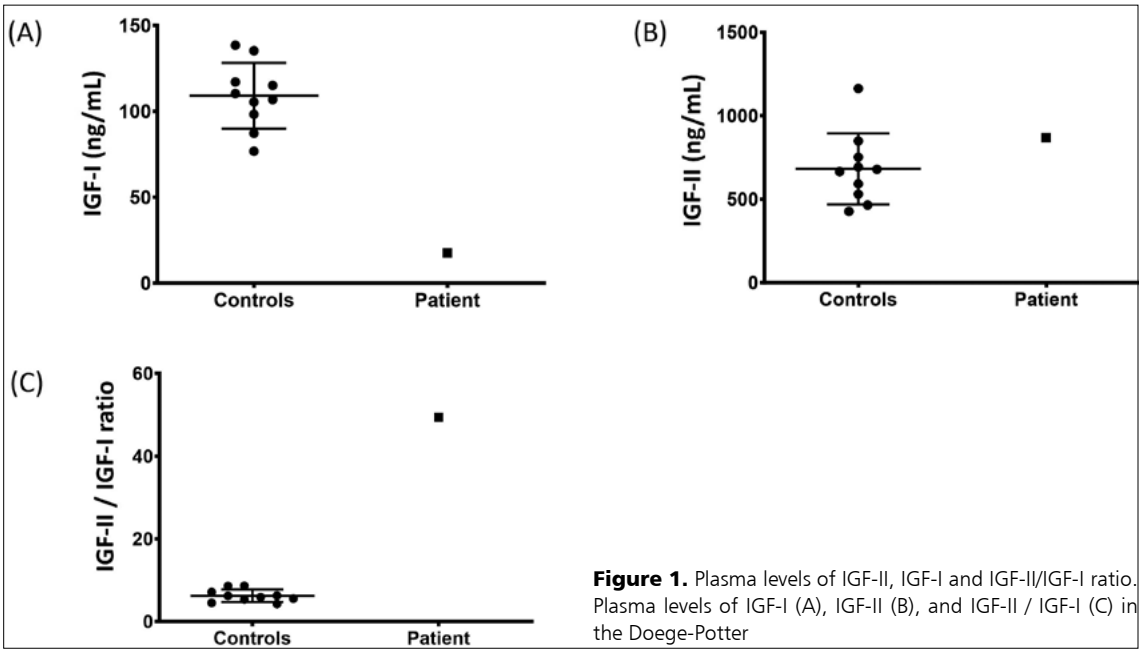


Figure 1. Plasma levels of IGF-II, IGF-I and IGF-II/IGF-I ratio. Plasma levels of IGF-I (A), IGF-II (B), and IGF-II / IGF-I (C) in the Doege-Potter

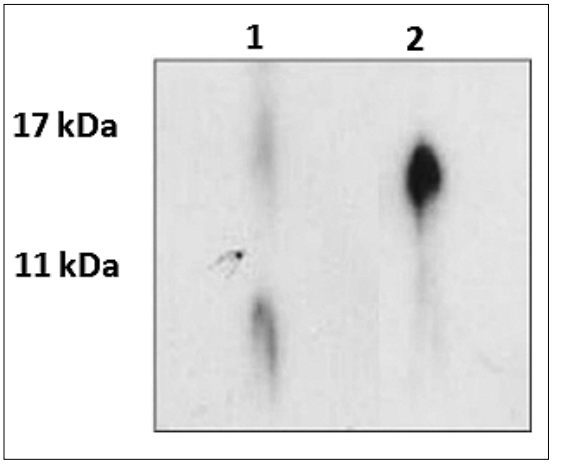
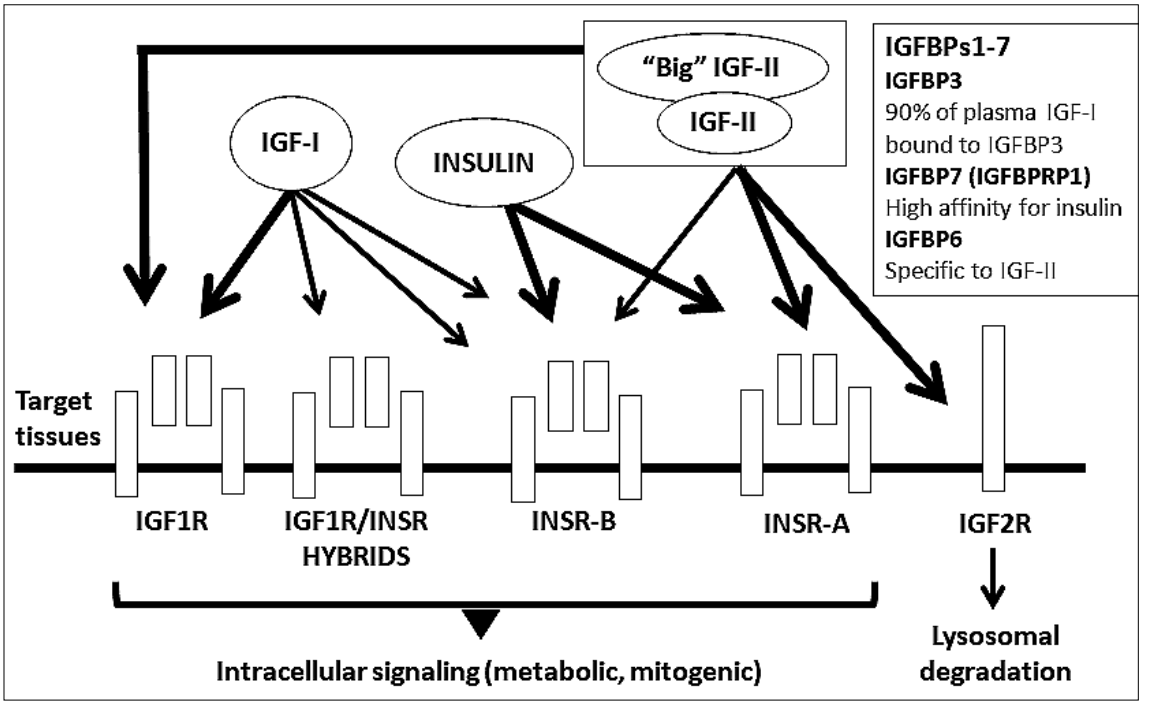


Figure 2. Identification of "Big IGF-II" forms in plasma and the insulin/IGF system. A. Western-blot in plasma: sample 1 corresponds to a control plasma, with a diffuse signal observed under the 11KDa corresponding to IGF-II. Sample 2: patient's plasma (diluted 1:10) showing a diffuse band corresponding to the high-molecular weight ("Big") forms of IGF-II. B. The insulin/IGF system including "Big IGF-II" and receptors.



with pro-insulin[16,17], and is located immediately adjacent (1.4 kb) to the INS gene at 11p[16]. IGF2 was one of the first genes identified to be imprinted, with paternal allelic expression and very low circulating levels in adult mice[16]. In contrast, human IGF2 gene and protein expression are maintained in humans throughout life with high circulating IGF-II levels during adulthood, which is possibly attributed to partial loss of imprinting and/or promoter activity in multiple tissues[16-20]. Moreover, IGF-II actions are regulated by its binding to soluble IGF binding proteins (IGFBPs 1-7, with IGF-II specificity to IGFBP6). Secretion of larger forms of IGF-II ("Big IGF-II"; ~10-18 kDa) encompass incomplete proteins of variable degree of glycosylation. Similar to mature IGF-II, "Big IGF-II" signals mainly to the IGF-I receptor, the type A insulin receptor (IR-A: splice variant of the insulin receptor lacking exon 11, signaling to mitogenic activity) and, to a lesser extent, to the type B insulin receptor (IR-B: splice variant of the insulin receptor including exon 11, signaling to

metabolic pathways)[19,20] (Figure 2B). Additionally, IGF-II binds to its specific IGF-II receptor, which is considered as a clearance receptor directing IGF-II to lysosomal degradation[17-20].

In conclusion, we have identified the high-molecular weight form of IGF-II in the plasma of a Chilean case of Doege-Potter syndrome with a resection of a solitary fibrous tumor. We have also shown that plasma IGF-II/IGF-I ratio is a better indicator of metabolic impairments of this syndrome compared to isolated measurements of circulating IGF-II or IGF-I levels.

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References

1. Bodnar TW, Acevedo MJ, Pietropaolo M. Management of non-islet-cell tumor hypoglycemia: a clinical review. J Clin Endocrinol Metab 2014; 99: 713–22.
2. Han G, Zhang Z, Shen X, Wang K, Zhao Y, He J, et al. Doege-Potter syndrome A review of the literature including a new case report. Medicine (Baltimore) 2017; 96: e7417.
3. Kalebi AY, Hale MJ, Wong ML, Hoffman T, Murray J. Surgically cured hypoglycemia secondary to pleural solitary fibrous tumour: Case report and update review on the Doege-Potter syndrome. J Cardiothorac Surg 2009; 4: 1–8.
4. Meng W, Zhu HH, Li H, Wang G, Wei D, Feng X. Solitary fibrous tumors of the pleura with Doege-Potter syndrome: A case report and three-decade review of the literature. BMC Res Notes 2014; 7: 515.
5. Dynkevich Y, Rother KI, Whitford I, Qureshi S, Galiveeti S, Szulc AL, et al. Tumors, IGF-2, and hypoglycemia: insights from the clinic, the laboratory, and the historical archive. Endocr Rev 2013; 34: 798–826.
6. Otake S, Kikkawa T, Takizawa M, Oya J, Hanai K, Tanaka N, et al. Hypoglycemia Observed on Continuous Glucose Monitoring Associated With IGF-2-Producing Solitary Fibrous Tumor. J Clin Endocrinol Metab 2015; 100: 2519–24.
7. Schmitt S, Ren-Qiu Q, Torresani T, Doebeli M, Zapf J, Schoenle EJ. High molecular weight forms of IGF-II ("big-IGF-II') released by Wilms" tumor cells. Eur J Endocrinol 1997; 137: 396-401.
8. Teale JD, Marks V. Inappropriately elevated plasma insulin-like growth factor ii in relation to suppressed insulin-like growth factor i in the diagnosis of non-islet cell tumour hypoglycaemia. Clin Endocrinol (Oxford) 1990; 33: 87–98.
9. León F. F, Bannura Y. F, Solovera R. ME, Salas P. P. Tumor fibroso solitario de la pleura asociado a síndromes paraneoplásicos. Rev Chil Cir. 2013; 65:255–9.
10. Soutelo J, Moldes S, Martin A, Lutfi R, Leal Reyna M. Hipoglicemia inducida por tumor fibroso solitario pulmonar. Síndrome de doege-potter. Rev Med Chile 2016;144: 129–33.
11. Campos MR, González LR, Saldías FR, Klaassen PR, Alarcón CE. Síndrome de Doege-Potter: hipoglicemia secundaria a tumor fibroso solitario de la pleura. Rev Med Chile. 2012; 140: 353-7.
12. Santolaya R, Meneses C, López J, Prats R, Fica M, González C, et al. Tumor fibroso solitario de la pleura: Análisis de 41 casos. Rev Chil Enf Respir 2007; 23: 11–6.
13. Ibaceta R, Salinas L, Strodtoff K. Hipoglicemia inducida por tumor fibroso solitario: a propósito de un caso clínico. Síndrome de Doege-Potter. XXVIII Congreso Chileno de Endocrinología y Diabetes (SOCHED). Puerto Varas, Chile. 9-10 Noviembre 2017. TL125.
14. Chamberlain MH, Taggart DP. Solitary fibrous tumor associated with hypoglycemia: an example of the Doege-Potter syndrome. J Thorac Cardiovasc Surg 2000; 119: 185–7.
15. Herrmann BL, Saller B, Kiess W, Morgenroth K, Drochner K, Schroder T, et al. Primary malignant fibrous histiocytoma of the lung: IGF-II producing tumor induces fasting hypoglycemia. Exp Clin Endocrinol Diabetes 2000; 108: 515-8.
16. Belfiore A, Rapicavoli RV, Le Moli R, Lappano R, Morrione A, De Francesco EM, Vella V. IGF2: A role in metastasis and tumor evasion from immune surveillance? Biomedicines 2023; 11: 229.
17. Holly JMP, Biernacka K, Perks CM. The neglected Insulin: IGF-II, a metabolic regulator with implications for diabetes, obesity, and cancer. Cells 2019; 8: 1207.
18. Sélénou C, Brioude F, Giabicani E, Sobrier ML, Netchine I. IGF2: development, genetic and epigenetic abnormalities. Cells 2022; 11: 1886.
19. Blyth AJ, Kirk NS, Forbes BE. Understanding IGF-II Action through insights into receptor binding and activation. Cells 2020; 9: 2276.
20. Rotwein P. The complex genetics of human insulin-like growth factor 2 are not reflected in public databases. J Biol Chem 2018; 293: 4324-4333.