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Longitudinal changes in maternal serum 1,25-dihydroxyvitamin D and insulin like growth factor I levels in pregnant women who developed preeclampsia: comparison with normotensive pregnant women☆

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Abstract

This study was undertaken to determine the longitudinal changes of serum 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D) and insulin like growth factor I (IGF-I) levels at 20.7, 27.6, and 35.5 week periods of gestation in 40 pregnant women who remained normotensive (NT) and in 10 women who developed preeclampsia (PE). As compared with the first period, significant increases ($P < 0.01$) in maternal serum 1,25-$(OH)_2$D and IGF-I were observed in the NT group. In the PE group, a similar increase in serum 1,25-$(OH)_2$D was observed. In contrast, significant ($P < 0.05$) lower IGF-I levels were observed in the PE group at the moment of diagnosis. In addition a high incidence of subjects with low increase in IGF-I levels (<percentile 10) was found in the PE group (30% versus 5%, $P = 0.02$). In conclusion, circulating levels of 1,25-$(OH)_2$D were not alterated in women before they developed PE. In the opposite, the high percentage of PE women with low increase in circulating IGF-I levels between the 20th and 35th week of pregnancy suggests early alterations of IGF-I synthesis in women developing PE.

Keywords: 1,25-dihydroxyvitamin D; Insulin like growth factor I; Preeclampsia

1. Introduction

It has been reported that insulin-like growth factor I (IGF-I) stimulates renal 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D) production in nonpregnant human and rodents [1–10]. In addition, previous results from this laboratory showed a stimulatory effect of IGF-I on placental 1,25-$(OH)_2$D synthesis [11,12], indicating that this growth factor could be a physiological regulator of Vitamin D metabolism during pregnancy. Preeclampsia (PE) is a pregnancy disorder characterized by hypertension and proteinuria [13]. Interestingly, in our previous studies [14,15], low maternal circulating levels of 1,25-$(OH)_2$D and IGF-I have been found in established PE. These observations prompted us to study longitudinal changes of 1,25-$(OH)_2$D and IGF-I serum levels in pregnant women who remained normotensive (NT) and to determine whether alterations in circulating levels of these two hormones could be observed in those women before they developed PE.

2. Materials and methods

2.1. Subjects

Maternal blood samples were obtained in accordance with the guidelines of the declaration of Helsinki, and the protocol of this study was approved by the Human Ethics Committee of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. The study was done longitudinally at three gestational periods (median: 20.7, 27.6, and 35.5 weeks) and included 170 healthy normotensive pregnant women. During this study, 160 women remained NT and 10 developed PE at the third gestational period (PE group), which corresponded to an incidence of 5.88%. Diagnosis of PE was based on the simultaneous presence of hypertension (systolic blood pressure ≥140 mm Hg and/or

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diastolic blood pressure ≥90 mm Hg) and marked proteinuria (at least 2+ on dipstick: >100 mg/dl) [13]. For each woman in the PE group, 4 NT women were chosen as controls. Ages, gestational ages, height and body weights were not significantly different between the NT group (40 women) and the PE group (10 women).

2.2. Methods

After extraction and subsequent purification using C18OH extra clean cartridges [16], 1,25-$(OH)_2$D concentrations were determined using ^{125}I RIA (DiaSorin, Stillwater, Minnesota, USA). Serum IGF-I were determined using an immunoradiometric assay kit (Diagnostic System Laboratories, Webster, TX, USA) after separation from its binding proteins, as previously described [17]. Serum IGF binding proteins, IGFBP-1 and IGFBP-3, were determined using immunoradiometric assay kits (Diagnostic System Laboratories, Webster, TX, USA). Serum human placental lactogen (hPL) was determined using a solid-phase RIA kit (Diagnostic Products Corporation, Los Angeles, CA, USA).

2.3. Statistical analysis

Results are presented as median with interquartile ranges. Analysis of statistical differences between groups and association between variables in each group were done using nonparametric tests.

3. Results

3.1. Longitudinal changes in hormones and IGF-binding proteins (IGFBPs)

Hormonal and IGF-binding protein concentrations at the three gestational periods in the NT and PE groups are shown in Table 1. At the first and second gestational periods, PE and NT groups were similar as regards to their 1,25-$(OH)_2$D, IGF-I, IGFBP-1, IGFBP-3 and human placental lactogen (hPL) levels. At the third period (median 35.5 weeks), IGF-I levels were significantly lower in the PE group, with no significant differences in the other variables tested. In addition, the highest incidence of women with a low increase in IGF-I was observed in the PE group (30% versus 5%, $P = 0.02$). A normal expected increase at the second and third periods in IGF-I was considered when serum IGF-I levels where above the 10th percentile of all women studied.

3.2. Association analysis

Correlation studies (Table 2) showed a significant association between 1,25-$(OH)_2$D and IGF-I levels in the NT group at all times tested, particularly at the second and third gestational periods. Significant correlations were also observed between IGF-I and IGFBP-3 at the second ($\rho = 0.59$, $P < 0.001$) and third ($\rho = 0.47$, $P < 0.01$) gestational periods. Similarly, IGF-I correlated significantly with hPL at the third gestational period ($\rho = 0.50$, $P < 0.01$). In the PE group, similar correlation coefficients were observed for the association between IGF-I and 1,25-$(OH)_2$D at the second gestational period ($\rho = 0.59$) and between IGF-I and IGFBP-3 at the first ($\rho = 0.59$) and second ($\rho = 0.60$) gestational periods without reaching statistical significance ($P = 0.08$), due to the small sample size. No association was found between hPL and IGF-I.

Table 1
Longitudinal changes of serum concentrations of hormones and IGFBPs in pregnant women who remained normotensive (NT group) and pregnant women who were diagnosed as preeclamptic (PE group) at the third gestational period

Variable	NT group ($n = 40$)	PE group ($n = 10$)	P
1,25-$(OH)_2$D (pg/ml)			
At the first GP	29 (24–36)	31 (26–34)	0.44
At the second GP	39 (34–45) c	43 (35–50) a	0.37
At the third GP	53 (45–62) c	55 (48–62) b	0.47
IGF-I (ng/ml)			
At the first GP	141 (109–194)	130 (86–190)	0.47
At the second GP	190 (140–235) b	144 (89–232)	0.27
At the third GP	271 (195–308) c	217 (90–260)	0.02
IGFBP-1 (ng/ml)			
At the first GP	106 (68–106)	107 (98–130)	0.51
At the second GP	117 (88–154) c	137 (125–155) a	0.36
At the third GP	164 (120–220) a	197 (165–242) b	0.21
IGFBP-3 (μg/ml)			
At the first GP	4.6 (4.0–5.3)	4.2 (3.6–4.6)	0.15
At the second GP	4.5 (4.1–5.2)	4.4 (3.8–5.0)	0.70
At the third GP	5.3 (4.3–5.8) b	5.3 (4.8–5.7) b	0.68
hPL (μg/ml)			
At the first GP	3.8 (2.8–5.5)	3.4 (3.0–6.0)	0.91
At the second GP	6.7 (6.0–9.5) c	6.7 (6.0–9.0) b	0.92
At the third GP	14 (11–15) c	13 (10–15) b	0.85

Values are given as median (interquartil range); a, b, and c, corresponded to P-values <0.05, <0.01 and <0.0001, respectively, as compared with the data observed at the firts gestational period (GP).

Table 2
Spearman rank correlations between 1,25-$(OH)_2$D and IGF-I concentrations at the first, second and third gestational periods (GP) observed in pregnant women who remained normotensive (NT group) and women who were diagnosed as preeclamptic (PE group) at the third gestational period

	NT group ($n = 40$)		PE group ($n = 10$)	
	ρ	P	ρ	P
At the first GP	0.30	0.09	0.28	0.40
At the second GP	0.58	0.0003	0.59	0.08
At the third GP	0.57	0.0004	−0.19	0.58

4. Discussion

Several studies have demostrated that IGF-I is a stimulatory factor of renal and placental 1,25-$(OH)_2$D synthesis

[1–12]. These observations prompted us to study longitudinal changes of 1,25-$(OH)_2$D and IGF-I serum levels in pregnant women who remained normotensive and to determine whether alterations in circulating levels of these two hormones could be observed in women before they developed PE. In the present study, maternal serum 1,25-$(OH)_2$D concentrations in the NT group increased significantly throughout the study periods. In pregnant women who developed PE, similar increases in serum 1,25-$(OH)_2$D concentrations were observed and no differences were found as compared to those in the NT group. This observation suggests that the Vitamin D-dependent components of intestinal calcium absorption [18–20] may not be altered before and at the moment of PE diagnosis. In the present prospective study, we could not follow 1,25-$(OH)_2$D changes up to delivery for ethical reasons, since all PE women underwant treatment with $MgSO_4$, which is known to result in Vitamin D metabolism alterations [21]. In any case, the present results exclude circulating 1,25-$(OH)_2$D levels as an early maker for the disease and the low circulating levels of 1,25-$(OH)_2$D seen during the time course of PE [14,15,22–24] may be considered as a secondary event, probably resulting from decreased renal and/or placental 1,25-$(OH)_2$D synthesis. Indeed, we previously reported that expression and activity of 25-hydroxyvitamin D-1α-hydroxylase are restricted in cultures of human syncytiotrophoblast cells from PE pregnancies [12]. The finding in other studies [25,26] of higher IGF-I levels in women who developed PE led to the suggestion that these women have an exaggerated IGF-I responsiveness compared to normotensive women. The present data do not confirm these observations. In the opposite, circulating IGF-I levels were not significantly different between NT and PE groups before PE development, and were even significantly lower at the time of diagnosis in the PE group. Furthermore, the physiological increase in IGF-I during pregnancy was altered in the PE group, with a markedly higher percentage of women with low IGF-I increase (30% versus 5%). This observation may explain, at least in part, the well known high incidence of babies small for gestational age born from PE women [15,27]. During normal pregnancy, it has been reported that placental growth hormone (GH) and hPL act in concert to stimulate IGF-I production and modulate intermediary metabolism, resulting in an increase on the availability of nutrients to the fetus [28]. In the present study, the absence of a significant increase of IGF-I levels in the PE group could no be explained by hPL, since changes of circulating levels of this hormone were similar in the NT and PE groups. Another hypothesis could be that the reduced IGF-I levels found in the PE group resulted from a decreased placental GH synthesis [29], which circulating levels were not assessed in the present work and deserve to be further investigated. IGF-I circulates in blood bound to six IGFBPs that modulate IGF-I action by enhancing or inhibiting its effects [30]. The finding in this study of similar serum concentrations of IGFBP-1 and IGFBP-3 in the NT and PE groups, and the low increase in IGF-I levels in the PE group, may indicate decreased IGF-I bioavailability in pregnant women who are at risk of developing PE.

In conclusion, maternal circulating levels of 1,25-$(OH)_2$D were not alterated in women before they developed PE. In the opposite, the high percentage of PE women with low increase in circulating IGF-I levels between the 20th and 35th week of pregnancy suggests early alterations of IGF-I synthesis in women developing PE.

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References

[1] T. Nesbitt, M.K. Drezner, Insulin-like growth factor-I regulation of renal 25-hydroxyvitamin D-1-hydroxylase activity, Endocrinology 132 (1) (1993) 133–138.
[2] R.W. Gray, Evidence that somatomedins mediate the effect of hypophosphatemia to increase serum 1,25-dihydroxyvitamin D_3 levels in rats, Endocrinology 121 (2) (1987) 504–512.
[3] B.P. Halloran, E.M. Spencer, Dietary phosphorus and 1,25-dihydroxyvitamin D metabolism: influence of insulin-like growth factor I, Endocrinology 123 (3) (1988) 1225–1229.
[4] J. Caverzasio, C. Montessuit, J.P. Bonjour, Stimulatory effect of insulin-like growth factor-1 on renal Pi transport and plasma 1,25-dihydroxyvitamin D_3, Endocrinology 127 (1) (1990) 453–459.
[5] L. Condamine, C. Menaa, F. Vztosnik, G. Friedlander, M. Garabedian, Local action of phosphate depletion and insulin-like growth factor 1 on in vitro production of 1,25-dihydroxyvitamin D by cultured mammalian kidney cells, J. Clin. Invest. 94 (4) (1994) 1673–1679.
[6] C. Menaa, F. Vrtovsnik, G. Friedlander, M. Corvol, M. Garabedian, Insulin-like growth factor I, a unique calcium-dependent stimulator of 1,25-dihydroxyvitamin D_3 production, J. Biol. Chem. 270 (43) (1995) 25461–25467.
[7] M.S. Wong, S. Sriussadaporn, V.A. Tembe, M.J. Favus, Insulin-like growth factor I increases renal 1,25-$(OH)_2D_3$ biosynthesis during low-P diet in adult rats, Am. J. Physiol. 272 (6 Pt 2) (1997) F698–F703.
[8] T. Bianda, M.A. Hossain, Y. Glatz, R. Bouillon, E.R. Froesch, C. Schmid, Effects of short-term insulin-like growth factor-I or growth hormone treatment on bone turnover, renal phosphate reabsorption and 1,25-dihydroxyvitamin D_3 production in healthy man, J. Int. Med. 241 (2) (1997) 143–150.
[9] T. Bianda, Y. Glatz, R. Bouillon, E.R. Froesch, C. Schmid, Effects of short-term insulin-like growth factor-I (IGF-I) or growth hormone (GH) treatment on bone metabolism and on production of 1,25-dihydroxycholecalciferol in GH-deficient adults, J. Clin. Endocrinol. Metabol. 83 (1) (1998) 81–87.
[10] S. Wei, H. Tanaka, Y. Seino, Local action of exogenous growth hormone and insulin-like growth factor-I on dihydroxyvitamin D production in LLC-PK1 cells, Eur. J. Endocrinol. 139 (4) (1998) 454–560.
[11] A. Halhali, L. Díaz, I. Sánchez, M. Garabedian, H. Bourges, F. Larrea, Effects of IGF-I on 1,25-dihydroxyvitamin D_3 synthesis by human placenta in culture, Mol. Hum. Reprod. 5 (8) (1999) 771–776.
[12] L. Díaz, C. Arranz, E. Avila, A. Halhali, F. Vilchis, F. Larrea, Expression and activity of 25-hydroxyvitamin D-1α-hydroxylase are restricted in cultures of human syncitiotrophoblast cells from

preeclamptic pregnancies, J. Clin. Endocrinol. Metabol. 87 (8) (2002) 3876–3882.
[13] National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy, Report of the National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy, Am. J. Obstet. Gynecol. 183 (1) (2000) S1–S22.
[14] A. Halhali, H. Bourges, A. Carrillo, M. Garabedian, Lower circulating insulin-like growth factor I and 1,25-dihydroxyvitamin D levels in preeclampsia, Rev. Invest. Clin. 47 (4) (1995) 259–266.
[15] A. Halhali, A.R. Tovar, N. Torres, H. Bourgues, M. Garabedian, F. Larrea, Preeclampsia is associated with low circulating levels of insulin-like growth factor I and 1,25-dihydroxyvitamin D in maternal and umbilical cord compartments, J. Clin. Endocrinol. Metabol. 85 (5) (2000) 1828–1833.
[16] B.W. Hollis, Assay of circulating 1,25-dihydroxyvitamin D involving a novel single-cartridge extraction and purification procedure, Clin. Chem. 32 (11) (1986) 2060–2063.
[17] W.H. Daughaday, I.K. Mariz, S.L. Blethen, Inhibition of access of bound somatomedin to membrane receptor and immunobinding sites: a comparison of radioreceptor and radioimmunoassay of somatomedin in native and acid-ethanol-extracted serum, J. Clin. Endocrinol. Metabol. 51 (4) (1980) 781–788.
[18] C.S. Kovacs, H.M. Kronenberg, Maternal-fetal calcium and bone metabolism during pregnancy, puerperium, and lactation, Endocrinol. Rev. 18 (6) (1997) 832–872.
[19] R.P. Heaney, M.J. Barger-Lux, M.S. Dowell, T.C. Chen, M.F. Holick, Calcium absorptive effects of vitamin D and its major metabolites, J. Clin. Endocrinol. Metabol. 82 (12) (1997) 4111–4116.
[20] G. Jones, S.A. Strugnell, H.F. DeLuca, Current understanding of the molecular actions of vitamin D, Physiol. Rev. 78 (4) (1998) 1193–1231.
[21] D.P. Kruikshank, G.M. Chan, D. Doerrfeld, Alterations in vitamin D and calcium metabolism with magnesium sulfate treatment of preeclampsia, Am. J. Obstet. Gynecol. 168 (4) (1993) 1170–1176.
[22] P. August, B.G. Marcaccio, J.M. Gertner, M.L. Druzin, L.M. Resnick, J.H. Laragh, Abnormal 1,25-dihydroxyvitamin D metabolism in preeclampsia, Am. J. Obstet. Gynecol. 166 (4) (1992) 1295–1299.
[23] E.W. Seely, R.J. Wood, E.M. Brown, S.W. Graves, Lower serum ionized calcium and abnormal calciotropic hormone levels in preeclampsia, J. Clin. Endocrinol. Metabol. 74 (6) (1992) 1436–1440.
[24] A. Tolaymat, L. Sanchez-Ramos, A.L. Yergey, N.E. Vieira, S.A. Abrams, P. Edelstein, Pathophysiology of hypocalciuria in preeclampsia: measurement of intestinal calcium absorption, Obstet. Gynecol. 83 (2) (1994) 239–243.
[25] M. Sowers, T. Scholl, J. Grewal, X. Chen, M. Jannausch, IGF-I, osteocalcin, and bone change in pregnant normotensive and pre-eclamptic women, J. Clin. Endocrinol. Metabol. 86 (12) (2001) 5898–5903.
[26] W.A. Grobman, R.R. Kazer, Serum insulin, insulin-like growth factor-I, and insulin-like growth factor binding protein-1 in women who develop preeclampsia, Obstet. Gynecol. 97 (4) (2001) 521–526.
[27] P.A. Long, D.A. Abell, N.A. Beischer, Fetal growth retardation and preeclampsia, Br. J. Obstet. Gynaecol. 87 (1) (1980) 13–18.
[28] S. Handwereger, M. Freemark, The roles of placental growth hormone and placental lactogen in the regulation of human fetal growth and development, J. Pediatr. Endocrinol. Metabol. 13 (4) (2000) 343–356.29.
[29] L.C. Giudice, N.A. Martina, R.A. Crystal, S. Tazuke, M. Druzin, Insulin-like growth factor binding protein-1 at the maternal-fetal interface and insulin-like growth factor-I, insulin-like growth factor-II, and insulin-like growth factor binding protein-1 in the circulation of women with severe preeclampsia, Am. J. Obstet. Gynecol. 176 (4) (1997) 751–758.
[30] J.I. Jones, D.R. Clemmons, Insulin-like growth factors and their binding proteins: biological actions, Endocr. Rev. 16 (1) (1995) 3–34.