Prematurity and maternal health conditions influence plasma glucose and triglyceride levels in newborns at six months of corrected age

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ABSTRACT

In the present study we evaluated growth, glucose and lipids homeostasis in preterm (PT) infants at birth and at 6 months of corrected age (6m of CA) and correlated with maternal health conditions. This was a longitudinal prospective study conducted between May 2015 and February 2017 with PT (n=71) and full term (FT) infants(n=82) and their respective mothers in a public hospital at south of Brazil. At birth, PT-infants showed, reduced growth parameters, high levels of glucose, insulin but lower triglyceride levels when compared to FT-infants. Only glucose remained elevated in PT-infants at 6m of CA; an effect correlated significantly with higher maternal body weight gain and with high degree of prematurity. In contrast, elevated maternal insulin plasma level was correlated with smaller glycemia of PT-infants at 6 m of CA. Moreover, in association, elevated maternal body weight gain during pregnancy, greater values of plasma glucose, insulin and cholesterol and high degree of prematurity were positively correlated with high plasma triglyceride levels in PT-infants at 6 m CA. In conclusion, this study confirms that maternal body weight gain and their metabolic state, as well as, the degree of prematurity are elements that affect glycemia and trigliceridemia in PT infants at 6 m CA. Glucose and lipid homeostasis at birth and infancy can determine onset of chronic diseases in adult life. Thus, PT-infants and their mothers should be more strictly accompanied to preserve health in future.

Keywords: Pregnancy, Prematurity, Glucose, Lipids, Metabolic Programming.
INTRODUCTION

Preterm (PT) birth constitutes a worldwide health problem having significant impact on infant mortality and morbidity and direct relationship with elevated risk for the development of neurological, sensory, respiratory and motor disabilities later on in life (Crump, 2020). However, in the last decade chronic diseases, such as, diabetes, hypertension, dyslipidemia and cardiovascular dysfunctions also have been observed more frequently in adult born PT, indicating that prematurity is a programming event (Crump, 2019).

According with the concept of the Developmental Origins of Health and Disease (DoHaD), early life environment exerts modulatory role on gene expression establishing as metabolic and neuronal pathways will respond in adulthood (Simeoni et al., 2018). Thus, modification in nutritional, hormonal or stressor events during pregnancy, lactation and early infancy can determine the risk of chronic diseases from childhood to adulthood (Storme et al., 2016). In this regard, the prematurity is an event that alters a critical period of development having implications for health state over the long term (Crump, 2020). Infants born PT frequently present a small size at birth, in association with rapid growth rates (catch-up) during childhood; both events are directly related to risks for the development of obesity and diabetes later in life (Singal, 2017). The infant born PT has a greater difficulty in preserving glucose homeostasis during the first few days of life, in particular due to limited glycogen stores, lower gluconeogenic hormone activities, and decreased hormonal responses, particularly of cortisol and insulin (Abramowski et al., 2020). In this context, several studies have shown that plasma glucose and insulin levels were higher in PT than in full term (FT)-infants (Ahmad et al. 2016) and presented associations with disease conditions at 2 years of age (Payal et al., 2016). Moreover, premature newborns frequently present alterations in lipids profile, event that could be related to the origins of atherosclerosis during early life (Sreekarthik et al., 2015). Adults born premature present a major risk for the development of type 2 diabetes (T2D) (Crump, 2020).

Similarly, maternal health conditions have a clear impact on hormonal and metabolic state of infant at birth, including prematurity (Catalano & Shankar, 2017). In this context, excessive or inadequate body weight gain (Xiao et al., 2017), hyperglycemia, dyslipidemia (Moayeri et al., 2017), hypertension (Guedes- Martins, 2016) or urinary tract infection (Bavaresco et al., 2019) during gestation contributes to cause PT birth. Moreover, maternal health state did not have just an immediate impact on the PT infant, but also contribute to disease risk later in life (Catalano & Shankar, 2017). In the present study we evaluated growth, glucose and lipids homeostasis in preterm (PT) infants at birth and at 6 months of corrected age (6 m of CA) and correlated with maternal health conditions at delivery.
METHOD

Ethic aspects

This is a cross-sectional and prospective study conducted from May 2015 to February 2017 in a public maternity hospital in south Brazilian region. The study was approved by the Institutional Human Ethics Committee of the University of Western Parana n. 1.134.712, Parana, Brazil and CAAE 16348813.7.1001.0107. The PT births were defined as newborns born at less than 37 weeks of gestational age (GA), while newborns born at ≥37 weeks of GA were considered FT according to the Brasil 2012. Informed consent was obtained from mothers and mothers who refused to participate in the study were excluded from the study.

Experimental design

The study was performed with four experimental groups: FT-infants and mothers-FT (control groups) and PT-infant and mothers-PT. In the FT groups, were included those pregnant >18 years old, without diabetes or hypertension and their respective FT infants, born without congenital anomalies and metabolic abnormalities and not exposed to phototherapy. In PT groups were included those infants born without congenital anomalies, that remained in the Intensive Therapy Unit (ITU) for more than 7 days. Independent of groups, mother and infants with insufficient blood sample and those who did not return at follow up were excluded. Thus, after the exclusion criteria, 67 mothers-PT and 82 mothers-FT were included with their respective infants (PT-infant 71; FT-infant 82).

Anthropometric data collection

Maternal heights (m²) and body weight (BW; Kg) were registered at pre-pregnancy (pp) and at last query (lq) to calculate body mass index (BMI; kg/m²) classified according Atalah (Brasil 2004). The total body weight gain (BWΔ) was obtained from the difference between ppBW–lqBW and expressed by Gestational Age (GA) (Brasil, 2004). The infants were evaluated at birth, being registered the body weight (g), height (cm) and cephalic circumference (CC) and the classification in Adequate for GA (AGA); Small for GA (SGA) and Larger for GA (LGA) was done according Fenton (Brasil, 2004). At six months of age for the FT-infants or corrected age (CA) for the PT-infants, anthropometric variables (body weight, height and CC) were reevaluated.
Blood collection and analysis

Maternal blood sample was collected at the time of hospitalization while the infant’s blood samples were collected between 24-72 hours after delivery and at 6 m of CA. Blood samples were submitted to biochemical analysis of glucose, triglycerides and total cholesterol determined by the dry chemistry method in an automated VITROS 4600 by Ortho Clinical Diagnosis, the data were expressed in mg/dL. Insulin (µUI/mL) was analyzed by the Electrochemiluminescence in an automated UniCelDxI 800, Beckman Coulter, using an Access Ultrasensitive Insulin immunoassays system (Beckman Coulter) and the limit of detection of insulin assay was 0.03 µUI/mL. In infants (PT and FT) the difference between the anthropometric and metabolic values at birth and at 6 m of CA was denominated of delta (Δ).

Statistical analysis

Data are expressed as mean ± standard deviation (SD) and the difference between groups (FT and PT) evaluated by unpaired t test or Mann-Whitney U test, according to the previously performed normality (Shapiro-Wilk) analysis. Generalized Linear Models (GLM) was applied to describe a potentially nonlinear relationship between maternal predictor terms and a plasma biochemical variable of infants at 6m of CA. The R version 3.3.2 (Since Pumpkin Patch); p <0.05 was used for all analyses.

RESULTS AND DISCUSSION

Maternal anthropometric and metabolic profile are showed in Table 1. At pre-pregnancy (pp) moment Mothers-PT and Mothers-FT showed similar BW, height and BMI (p>0.05). However, at last query (lq), the Mothers-PT presented smaller BW, BW gain, and BMlin relation to Mothers-FT (p<0.05). In consequence the fluctuation of BMI (Δ) at long of pregnancy was smaller in Mothers-PT in comparison at Mothers-FT (p<0.05). At delivery, the glycemia, triglyceridemia and insulinemia were similar in maternal groups. However, total plasma cholesterol levels were smaller in Mothers-PT in relation to Mothers-FT (Table 1; p<0.05).
Table 1. Maternal anthropometric and metabolic characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Mothers-PT (n=67)</th>
<th>Mothers-FT (n=82)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ppBW (Kg)</td>
<td>65±14</td>
<td>67±14</td>
<td>0.257*</td>
</tr>
<tr>
<td>lqBW (Kg)</td>
<td>72±14</td>
<td>80±14</td>
<td>0.003</td>
</tr>
<tr>
<td>BW gain (Kg)</td>
<td>8±6</td>
<td>13±7</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160±7</td>
<td>161±6</td>
<td>0.336</td>
</tr>
<tr>
<td>ppBMI</td>
<td>25±5</td>
<td>26±5</td>
<td>0.501*</td>
</tr>
<tr>
<td>lqBMI</td>
<td>28±5</td>
<td>31±5</td>
<td>0.008*</td>
</tr>
<tr>
<td>Δ BMI</td>
<td>3±2</td>
<td>5±3</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>102±40</td>
<td>96±32</td>
<td>0.568*</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>207±89</td>
<td>233±103</td>
<td>0.165*</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>202±50</td>
<td>233±52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insulin (µUI/mL)</td>
<td>23±33</td>
<td>21±25</td>
<td>0.643*</td>
</tr>
</tbody>
</table>

Data are mean±SD. BW: body weight; pp=pre-pregnancy; lq=last query; BMI= body mass index; * Mann-Whitney-U.

The anthropometric characteristics of newborns at birth and at 6 m of CA are shown in Table 2. At birth and at 6m of CA the PT-infants presented significant reductions in BW; height and CC in relation to FT-infants. However, from birth to 6m the BW, CC and height gain (Δ) were higher in PT-infants in relation to FT-infants (Table 2; p<0.0001).

Table 2. Anthropometric characteristics of infant groups at birth and at 6m of CA.

<table>
<thead>
<tr>
<th></th>
<th>PT-infants (n=71)</th>
<th>FT-infants (n=82)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BW (g)</td>
<td>1609±623</td>
<td>3240±442</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>40±4</td>
<td>48±2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CC (cm)</td>
<td>29±3</td>
<td>34±2</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>At 6 m of CA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BW (g)</td>
<td>7074±1262</td>
<td>7892±843</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>65±3</td>
<td>67±3</td>
<td>0.005*</td>
</tr>
<tr>
<td>CC (cm)</td>
<td>42±2</td>
<td>44±1</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Δ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BW (g)</td>
<td>5464±953</td>
<td>4651±705</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>25±3</td>
<td>18±2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CC (cm)</td>
<td>14±3</td>
<td>10±2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are mean±SD; BW= body weight; CC= cephalic circumference; BW * Mann-Whitney-U Test.

The metabolic biochemical profiles of newborns at birth and at 6 m of CA are shown in Figure 1. At birth, plasma levels of glucose (Fig. 1A) and insulin (Fig. 1J) were significantly greater in PT-infants compared to FT-infants (p<0.05). In contrast, at this moment, the plasma triglycerides levels were lower in PT-infants compared to FT-infants (Fig. 1D; p<0.05) without significant difference in total cholesterol values (Fig. 1G; p>0.05). At 6m of CA only glycemia remained slight elevated in PT-infants in comparison to FT-infant group (Fig. 1B; p<0.05). The other metabolic variables were similar between infant groups at 6m of CA (Fig. 1E; 1H and 1K; p>0.05). However, the delta (Δ) values of biochemistry plasmatic variables were influenced by prematurity. Thus, from birth to 6m of CA, PT-infants showed reduction in glucose (Fig. 1C) and insulin levels (Fig. 1L) associated with elevation in triglycerides plasma
levels (Fig. 1F) in relation to FT-infants (p<0.05). The delta of total cholesterol (Fig. 1I) was similar between groups (p>0.05).

**Figure 1.** Plasma metabolic parameters in newborns at birth and at 6 m of CA.

Data are mean±SD; PT-infants, n=71 and FT-infants, n=82. The plasma values for each biochemical variable at birth are shown in Figures 1A, 1D, 1G, 1J and at 6 m of CA in Figures 1B, 1F, 1H, 1K. The delta (Δ) was obtained as the difference between values at birth minus the values at 6 m of CA and are shown in Figures 1C, 1F, 1I, 1L. *p<0.05.

In FT-infants no were found significant correlation between maternal characteristics and anthropometric or metabolic state at 6m of CA. However, in PT-infants, the prematurity degree and maternal health condition had repercussion in the plasmatic values of glucose and triglycerides at 6m of CA. Thus, elevated degree of prematurity and high maternal BW gain
throughout gestation were positively correlated with elevated glycemia in PT-infants at 6 m of CA (Table 3; p<0.05). In contrast, greater maternal plasma insulin levels at delivery were related with reduced glycemia in PT-infants at 6 m of CA (Table 3; p<0.05).

### Table 3. Correlation between maternal condition and prematurity with glycemia levels in PT-Infants at 6 m of CA.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>T</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>67.52794</td>
<td>4.92887</td>
<td>13.70</td>
<td>&lt;2e-16***</td>
</tr>
<tr>
<td>BW gain</td>
<td>11.67753</td>
<td>4.95300</td>
<td>2.358</td>
<td>0.01980***</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.05053</td>
<td>0.02711</td>
<td>1.864</td>
<td>0.06446</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.01206</td>
<td>0.01092</td>
<td>-1.104</td>
<td>0.27147</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.02960</td>
<td>0.02064</td>
<td>1.434</td>
<td>0.15389</td>
</tr>
<tr>
<td>Insulin</td>
<td>-0.06736</td>
<td>0.03126</td>
<td>-2.155</td>
<td>0.03291*</td>
</tr>
<tr>
<td>Prematurity</td>
<td>5.83183</td>
<td>1.89013</td>
<td>3.085</td>
<td>0.00246 **</td>
</tr>
</tbody>
</table>

Moreover, if associated, greater degree of prematurity and maternal conditions such as, elevated BW gain, higher glycemia, insulinemia and plasma cholesterol levels results in significantly increased plasma triglyceride levels in PT-infant at 6 m of CA (Table 4).

### Table 4. Correlation between maternal condition and prematurity with triglycerides levels in PT-Infants at 6 m of CA.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>T</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-1.390e+03</td>
<td>1.802e+03</td>
<td>-0.771</td>
<td>0.4429</td>
</tr>
<tr>
<td>BWgain.G.I.</td>
<td>-3.909e-01</td>
<td>2.131e-01</td>
<td>-1.859</td>
<td>0.0703</td>
</tr>
<tr>
<td>BWgain.C.I.P</td>
<td>-2.105e-01</td>
<td>1.145e-01</td>
<td>-1.839</td>
<td>0.0698</td>
</tr>
<tr>
<td>BWgain.G.C.I.P</td>
<td>2.134e-03</td>
<td>1.1054e-03</td>
<td>2.024</td>
<td>0.0464*</td>
</tr>
<tr>
<td>BWgain.G.T.C.I.P</td>
<td>-1.118e-05</td>
<td>6.123e-06</td>
<td>-1.827</td>
<td>0.0716</td>
</tr>
</tbody>
</table>


## DISCUSSION

The relationship between mother and fetus during gestation involves metabolic and hormonal aspects that go beyond intrauterine development, and have immediate effects at birth, with consequences on health states over the long term (De Jong et al., 2014). In this context, the early disruption of glucose and lipid homeostasis is frequently associated with metabolic programming diseases later on in life, in special obesity, diabetes and hypertension (Kim et al., 2020).

Its well-recognized that anthropometric maternal conditions, such as body weight, height and BMI, are variables that can affect newborns at birth and have implications on their health in the long term. In our sample, at pre-pregnancy and at last query, both maternal groups presented overweight. Over weight and excessive fat mass during pregnancy are factors that can increase the risk for prematurity having long-term deleterious programming effect on descendant (Faucher et al., 2016; Mahizir, 2016). The body weight gain during pregnancy reflects, in part, on the duration of gestation (longer pregnancies allow more weight gain), which must be considered by calculating week-specific weight gain (Behrman & Butler 2007).
Using body weight gain by weeks, we demonstrated that despite being overweight Mothers-PT presented less body weight gain, in relation to Mothers-FT, during gestation (data no shown). Reduced body weight gain during gestation is a risk factor for PT delivery, as well as for the birth of babies with small gestational age (SGA) (Xiao et al., 2017; Enomoto et al., 2016). The frequency of SGA no was altered in our sample (data no shown).

Maternal metabolic conditions, particularly disruptions in glucose and lipids homeostasis, can affect neonate health at birth with repercussions a long life (Alsnes et al. 2017). In our study, Mothers-PT presented adequate plasma concentrations of glucose, insulin and tri-glycerides, but reduced plasma cholesterol levels in relation to Mothers-FT. Inadequate total cholesterol in mothers have been related to PT birth (Smith et al., 2018). In a case-control study, Catov et al., 2007 included only spontaneous PT and found an association between high maternal total cholesterol and very early PT. However, total cholesterol during early gestation was not associated with any of the outcome measures, including PT birth in a study carried out by Vrijkote et al. 2012. In addition, is important to recognize that, during normal pregnancy, women show an increase in lipid levels, including levels of triglycerides and total cholesterol as GA progresses (Pusukuru et al., 2016).

The relationship between prematurity and chronic diseases in adult life can be related to catch-up growth (Singhal, 2017). Frequently the catch-up growth begins during the first months of life and can be slow and progressive in PT-infants being independent risk factor for adverse health outcomes (Liu et al., 2017). In this sense, we observed that, from birth to 6m of CA, the growth parameters presented higher gain in PT-infants than in FT-infant, confirming growth catch-up. Importantly, accelerated catch-up is closely related to diseases later in life, including T2D (Liu et al., 2017) and therefore, alterations in glucose regulation have been proposed as a candidate for explaining this mechanism (Singal, 2017).

Premature neonates have difficulty in preserving glucose homeostasis (Abramowski et al., 2020), an event that could be related to increased risk of diabetes in adult life (Hovi, 2007). Adults born premature have higher fasting glucose levels, lower insulin sensitivity and higher blood pressure than adults born FT (Rerkasem et al., 2020; Rodriguez et al., 2020). The reduction in insulin sensitivity, as a result of premature birth, is already present in children between the ages of 4 and 10 years (Hofman, 2004). Our study, at birth PT infants presented higher glucose and insulin levels in comparison with FT-infants. Hyperglycemia was common and most severe among those born earliest and smallest (Turai et al., 2019). Interestingly, Scheurer et al. 2016 demonstrated a relationship between hyperglycemia at birth and later low growth at 4 m of CA in premature newborns. Using cord blood analysis in PT-infants, Ahmad et al. 2016 demonstrated that more premature neonates present greater plasma insulin levels.
At post-delivery, blood glucose levels fall in newborns, and there after, stabilization of glycemia is dependent on the activation of hepatic glycogenolyses and gluconeogenesis (Singhal, 2017). Transient disturbances in neonatal glucose homeostasis are common during this time, especially when metabolic reserves are low, as occurs in prematurity. PT-infants have lower hepatic glycogen reserves, lower activities of key gluconeogenic enzymes, and inadequate hormonal responses (Abramowski et al., 2020). Unfortunately, we did not measure insulin sensitivity, but our data show higher glucose and insulin in PT-infants at birth, suggesting insulin resistance. Corroborating this hypothesis, higher insulin and insulin resistance, measured by the HOMA index, was found in very PT-infants by Ahmad et al. 2016. Hyperinsulinemia in PT-infants is related to inappropriate glucose-induced insulin secretion from immature beta cell pancreas (Payal et al., 2016). Here in, we also demonstrated that PT-infant have smaller triglycerides levels at birth. Kwon et al. 2016 also found reduced triglyceride levels in PT-infants, compared to FT-infants, although they did not observe differences in glucose or insulin levels between FT-infants and PT-infants.

For the first time, we demonstrated that plasma glucose levels remained augmented at 6 m of CA, in prematurely born babies, suggesting difficulty in the preservation of glucose homeostasis during the early phase of infancy. Insulin resistance is a hallmark of T2D and is frequently observed in PT-infants that present catch-up during growth (Mericq et al., 2017). The body weight gain during the first 6 months of life was more strongly related to the risk of insulin resistance in adulthood, compared with body weight gain later on in infancy. Very low birth weight (VLBW) infants already have one or more components of metabolic syndrome at 2 years of CA (Payal et al., 2016). In our study, PT-infants at 6 m of CA presented growth catch-up and slight glucose elevation, suggesting metabolism dysfunctions. Importantly, we noted that, at long of first 6 months of life, the profile of metabolism was different modulated in PT and FT-infants. Thus, from birth to 6 m of CA, a gradual reduction in glycemia and plasma insulin accompanied of rises in plasma triglyceride levels was found in PT-infant, in contrast to observations in FT-infants. We believe that this shift in metabolism observed in premature newborns could be consider, a metabolic marker for diseases later on life.

To investigate the role of prematurity and maternal health state with metabolism of infants at 6m of CA we performed a linear regression analysis. According to our findings, the degree of prematurity of newborn, as well as, the maternal body weight gain during gestation were correlated with higher plasma glucose levels in PT-infants at 6 m of CA. Moreover, maternal conditions such as, greater body weight gain during pregnancy, high values of cholesterol, insulin, and plasma glucose levels at delivery associated with a higher degree of prematurity of newborn results in increased plasma triglyceride levels in PT- infants at 6 m of CA. To our knowledge, this is the first study to demonstrate a relationship between maternal conditions
and glucose and lipids homeostasis in PT-infants at 6 m of CA, an effect exclusively observed in the prematurity.

In conclusion, babies born PT show hyperglycemia, hyperinsulinemia and lower triglycerides levels at birth, presenting accelerated growth catch-up and several oscillations in metabolism at long of first six months of life. The maternal body weight gain during gestation and the degree of prematurity are elements that influence glucose in PT-infants at 6 m of CA. The association the maternal body weight gain with elevated values of glucose, insulin, total cholesterol and degree of prematurity results in high triglycerides level in PT-infant at 6m of CA. These new findings indicate that public system should to improve maternal health and metabolic profile of babies born premature to avoid chronic diseases development at long of life.

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■ AUTHOR CONTRIBUTIONS

Bruna Juliana Zancanaro Frizon, Ana Tereza Bittencourt Guimarães, Claudia Silveira Viera, Beatriz Rosana Gonçalves de Oliveira Toso, Sabrina Grassiolli, participate in the conception, design, analysis and interpretation of the data; writing of the manuscript and its revision, and in final approval of the version to be published. Grasielly Masotti Scalabrin Barreto, Hugo Razini de Oliveira, Talita Bavaresco, Álvaro Largura, participate in the design, analysis and interpretation of the data and in final approval of the version to be published.

■ CONFLICT OF INTEREST

None

■ REFERÊNCIAS


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