

Psychological Stress May Induce Diabetes-Related Autoimmunity in Infancy

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OBJECTIVE — In retrospective studies, a number of disparate environmental factors (including experiences of serious life events) have been proposed as trigger mechanisms for type 1 diabetes or the autoimmune process behind the disease. Psychosocial stress in families may affect children negatively due to a link to hormonal levels and nervous signals that in turn influence both insulin sensitivity/insulin need and the immune system. Our aim was to investigate whether psychological stress, measured as psychosocial strain in families, is associated with diabetes-related autoimmunity during infancy.

RESEARCH DESIGN AND METHODS — The first 4,400 consecutive 1-year-old children from a large prospective population-based project participated in the study. Parents completed questionnaires at birth and at 1 year, including various measures of psychosocial stress (e.g., parenting stress) and sociodemographic background. Blood samples drawn from the children at 1 year were analyzed for type 1 diabetes-associated autoantibodies toward tyrosine phosphatase and GAD. Antibodies toward tetanus toxoid were used as non-diabetes-related control antibodies.

RESULTS — Psychosocial factors, i.e., high parenting stress (odds ratio 1.8 [95% CI 1.2–2.9], $P < 0.01$), experiences of a serious life event (2.3 [1.3–4.0], $P < 0.01$), foreign origin of the mother (2.1 [1.3–3.3], $P < 0.001$), and low paternal education (1.6 [1.1–2.3], $P < 0.01$) were associated with diabetes-related autoimmunity in the child, independent of family history of diabetes.

CONCLUSIONS — Psychological stress, measured as psychosocial strain in the family, seems to be involved in the induction, or progression, of diabetes-related autoimmunity in the child during the 1st year of life.

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Type 1 diabetes is a multifactorial disease caused by an autoimmune destruction of insulin-producing β -cells, particularly in genetically predisposed individuals (1). At present, a com-

bination of high concentrations of tyrosine phosphatase autoantibodies (IA-2As) and GAD autoantibodies (GADAs) is considered to be the best (2) (and high concentrations of IA-2As alone the sec-

ond best [3]) marker of this autoimmune process. Various environmental hypotheses have been suggested concerning the trigger mechanisms, e.g., viral infections (1), the hygiene hypothesis (4), and the accelerator hypothesis (5). The accelerator hypothesis suggests that insulin resistance, due to extensive weight gain, is an accelerator of the β -cell destruction that leads to type 1 diabetes. However, psychological stress is another important source for insulin resistance. Moreover, there are also some risk factors not explained by these etiological hypotheses, e.g., low socioeconomic status (6) and parental age (7).

As early as in the middle of the 17th century, T. Wills suggested that nervous system juice and prolonged sorrow were important etiological factors in diabetes. More recently, events related to severe psychological stress have been reported as risk factors for type 1 diabetes in a nationwide Swedish case-referent study (8). Another retrospective study found that experiences of negative life events (e.g., separation of the parents, serious illness, or death in the family) during the first 2 years of life were more common in newly diseased diabetic children than in a control group (9). Recently, we reported associations between high parenting stress, lack of support/confidence, and some risk factors for type 1 diabetes, such as low socioeconomic status (10). We hypothesized that psychological factors may not only precipitate diabetes, but may also trigger or promote the progress of diabetes-related autoimmunity.

Previously, psychological stress has been linked to a number of negative health consequences, ranging from pain and sleep deficiencies to negative effects on cardiovascular, endocrine, and immune systems (11,12). It is also well known that psychological stress decreases insulin sensitivity, which in turn increases pressure on the β -cells (β -cell stress). According to the attachment theory, infants need to remain in physical proximity to their caregivers in order to survive, which in turn requires that infants be very sen-

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Abbreviations: ABIS, All Babies In Southeast Sweden; GADA, GAD autoantibody; IA-2A, tyrosine phosphatase autoantibody; SPSQ, Swedish Parenthood Stress Questionnaire.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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sitive to parental moods, signals, and behaviors (13). Hence, psychological stress in children might be caused by negative family circumstances, e.g., parenting stress, experiences of serious life events, unemployment, or low socioeconomic status, since the infants sense the stress experienced by the parents (14).

The aim of the current study was to investigate whether psychological stress, measured as psychosocial strain in families, is associated with the induction or progression of diabetes-related autoimmunity during infancy in the general population, i.e., irrespective of genetic risk for type 1 diabetes.

RESEARCH DESIGN AND METHODS

From 1 October 1997 to 1 October 1999, all parents-to-be in southeast Sweden were invited to participate in the All Babies In Southeast Sweden (ABIS) project, and 78.6% agreed, yielding a sample of 17,055 families at birth. In the current study, parental questionnaire responses from birth and 1 year as well as blood samples from 1 year were examined in the first 4,400 consecutive families for whom data were available for statistical analyses, i.e., no specific selection was made. The study cohort was representative of the full ABIS cohort at birth concerning parental age, educational level, and foreign origin. Compared with Sweden as a whole and the province of Östergötland, there was a slight underrepresentation of parents born abroad and parents with low education in the current sample (15).

Measures

The Swedish Parenthood Stress Questionnaire. The Swedish Parenthood Stress Questionnaire (SPSQ) (16) was used to measure parenting stress at 1 year. The SPSQ consists of 34 items, e.g., "It is more difficult than I expected to raise a child," "My life is more or less controlled by the needs of my child," and "Thanks to my child I have made several new acquaintances." The SPSQ was used with 6-point Likert-type response scales (range 1–6), and the stress score for each individual was calculated as a mean value of all SPSQ questions answered. In the current study, a relatively strict criterion (>95th percentile) was used to define the cutoff for high stress in order to compensate for a slight floor effect in the sample ($M = 2.59$ compared with a theoretical

mean of 3.5). The instrument has good internal validity (Cronbach's α for all subscales ≥ 0.65) and good test-retest reliability over 30 days (16).

Experiences of serious life events. Experiences of serious life events were assessed with two dichotomous (yes/no) questions, at birth: "Have you experienced something that you would describe as a serious life event (e.g., death of a close relative or divorce) during pregnancy?" and at 1 year: "Has your child experienced a serious or traumatic event (e.g., death in the family, divorce, new guardian, or the like)?"

Social support and confidence/security. Social support and confidence/security were assessed with two dichotomous (yes/no) questions at birth: "Do you experience enough support from your social environment for yourself and your newborn baby?" and "Do you feel that you have enough confidence/security so that you can give yourself and your newborn child a good start?" These rather crude measures were used to assure capturing of the mothers who truly lacked social support or confidence/security.

Additional psychological stress mechanisms. Additional psychological stress mechanisms measured in the questionnaires were as follows: foreign origin of the parent, defined as the mother or the father not born in Sweden (specified origin or race was not assessed); single parenthood, which was compared with cohabiting or married parents; low socioeconomic status, measured as low parental education, defined as only having finished 9-year compulsory school; parental unemployment (not maternity leave), registered during the child's 1st year of life; and need for neonatal intensive care (yes/no), assessed in the at-birth questionnaire.

Autoantibodies. IA-2As and GADAs were assessed in whole blood drawn from the child at 1 year of age. The blood samples were analyzed by an immunoprecipitation method (2). Positivity for IA-2As and GADAs was determined as antibody levels above the 95th percentile for 1-year-old healthy infants, which corresponds to 34.8 World Health Organization (WHO) units for IA-2A and 97.9 WHO units for GADA. Cutoffs at the 95th percentile yielded samples of 220 infants positive for IA-2A and 221 for GADA. Only 33 of these infants were double pos-

itive, i.e., positive for IA-2A as well as GADA.

In the 2nd international workshop (Diabetes Autoantibody Standardization Program, 2002), the specificity was 100% for the IA-2A and 96% for the GADA assay and the sensitivity was 54 and 81%, respectively. The intra-assay coefficient of variation (CV) was 5.2%, and the interassay CV was 13%.

Non-diabetes-related antibodies. Non-diabetes-related antibodies against tetanus toxoid were analyzed in a subgroup ($n = 721$) of the study population. The selection criteria were 1) lack of support, lack of confidence, and/or high parenting stress (i.e., above the 95th percentile on SPSQ; $n = 404$) and 2) social support, confidence/security, and low parenting stress (i.e., below the 5th percentile on SPSQ; $n = 317$).

Antibodies toward tetanus toxoid were detected with enzyme-linked immunosorbent assay. Tetanus toxoid (0.1 μg) in PBS was used for coating the plates, 0.05% Tween-PBS was used as washing buffer, and 1% human serum albumin in PBS was used as blocking agent. The whole-blood samples were studied at a dilution of 1/400 in 0.2% human serum albumin–0.05% Tween-PBS. Alkaline phosphatase-conjugated anti-human IgG (Fc) (Jackson ImmunoResearch) was used as a secondary antibody. The results were expressed as optical density units. A homemade standard was prepared from a pool of serum samples with high levels of antibodies to tetanus toxoid to control the interassay variation, which was 14%. The intra-assay variation was 9%.

Potential confounding factors. Potential confounding factors that might influence the occurrence of diabetes-related autoantibodies (1,7,17) were assessed in the questionnaires. Autoimmunity in the family was defined as a mother, father, or sibling suffering from hypo- or hyperthyroidism, pernicious anemia, SLE/LED/Lupus erythematosus, Mb Addison, Celiac disease, inflammatory bowel disease (Mb Crohn or Colitis ulcerosa), or rheumatoid arthritis. Type 1 diabetes in the family was defined as a mother, father, or sibling suffering from type 1 diabetes. Increased maternal/paternal age was defined as being >30 years at the time of the birth of the child. Early introduction of food (especially gluten and cow's milk) was controlled for by assessing the length, in months, of exclusive breast-feeding.

Size for gestational age was calculated according to the formula of the National Swedish Board of Health and Welfare, yielding the categories small, appropriate, or large for gestational age. The BMI of the child was calculated based on the height and weight reported by the parents at 1 year. Two groups, above and below the 90th percentile, were formed. Three different measures of child infections were assessed at 1 year. The number of gastroenteritis and infections treated with penicillin during the 1st year of life was dichotomized into three or more versus two or less. The number of upper respiratory infections was dichotomized into two or more versus one or none. Delivery mode was assessed at birth and coded as normal delivery versus cesarean section (all other types of problematic deliveries were excluded).

Procedure

The first questionnaire was completed by the parents during the child's 1st week of life. Capillary blood was drawn from the child, and the second questionnaire was given to the parents at the 1-year checkup at the well child clinics. The capillary tubes with whole blood were sent to and analyzed at the Clinical Research Centre, Faculty of Health Sciences, Linköping, Sweden.

Statistical analyses

SPSS 11.0 was used to calculate χ^2 values, Mann-Whitney analyses, Spearman's rank correlation coefficients (ρ), and logistic regression analyses. The initial univariate analyses were not corrected for multiple comparisons, despite repeated χ^2 analyses, since the risk of missing actual differences was regarded as more problematic than the risk of finding false differences concerning the selection of variables for inclusion in the multivariate analyses. However, the statistical significances found in the univariate analyses were still evaluated regarding their individual theoretical plausibility and concerning the uniformity of the patterns of results, since an expected pattern of results is more likely to indicate a true effect. Concerning the multivariate logistic regression analyses, only odds ratios with P values <0.01 were regarded as statistically significant in order to correct for multiple comparisons.

The findings were examined for a number of potential confounding factors;

if these were nonrelated to IA-2A, GADA, and double positivity, they could not explain our findings. The sample was also stratified for diabetes heredity, and the bivariate relation between parenting stress and autoimmunity was examined in the absence of diabetes heredity. Intercorrelations between the psychosocial variables associated with IA-2A and GADA, respectively, were investigated using Spearman's r (ρ). Multiple logistic regression analyses (forward stepwise) were conducted in order to differentiate among the psychosocial variables associated with IA-2A and GADA separately and, if needed, to investigate whether any potential confounding factors would be included in the regression models. Odds ratios (ORs) with 95% CIs were used as approximate measures of relative risk.

Ethical considerations

Participating parents gave their consent after receiving oral and written information, as well as having been offered to see a video film about the project. The parents were not automatically informed of the autoantibody status of their child. However, they were told that they could receive this information upon active request, but $<1\%$ of the parents have taken advantage of this possibility.

The ABIS project and the current study were approved by the Research Ethics Committees of the Faculty of Health Science at the University of Linköping, Linköping, Sweden, and the Medical Faculty at the University of Lund, Lund, Sweden.

RESULTS — A significant association between high parenting stress and concentrations of IA-2A above the 95th percentile was found (Table 1): 8.4% of those with high parenting stress were IA-2A positive [$\chi^2(1) = 11.133$, $P < 0.001$]. This association remained significant, even in the strata 1) without as well as with autoimmunity in the family and 2) without type 1 diabetes in the family. 1) In the strata without autoimmunity in the family ($n = 3,915$), 8.6% of those reporting high parenting stress were IA-2A positive [$\chi^2(1) = 9.929$, $P < 0.01$]. Concerning the strata with autoimmunity in the family ($n = 473$), 9.8% of those reporting high parenting stress were IA-2A positive. This distribution was almost equal to the distribution of the full sample and the strata without autoimmu-

nity in the family, but it did not reach statistical significance. 2) Concerning the strata without type 1 diabetes in the family ($n = 4,180$), 8.8% of those reporting high parenting stress were IA-2A positive [$\chi^2(1) = 11.331$, $P < 0.001$]. However, regarding type 1 diabetes in the family ($n = 109$), there were not enough subjects in the high stress group ($n = 4$) for statistical analysis.

In addition, the experience of a serious life event during the child's 1st year of life and maternal unemployment (not maternity leave) during the child's 1st year of life were significantly associated with concentrations of IA-2A above the 95th percentile (Table 1). There were very low correlations between the three psychosocial factors (strongest correlation: $\rho = 0.055$, $P < 0.01$) associated with increased concentrations of IA-2, and the multivariate logistic regression model included only parenting stress (OR 2.0 [95% CI 1.3–3.0], $P < 0.001$) as a predictor. The P value for experience of a serious life event during the child's 1st year of life (1.9 [1.1–3.3]) was 0.025; therefore it was disregarded as a predictor in this regression model due to the correction for multiple analyses.

With regard to concentrations of GADA above the 95th percentile, there were significant associations with foreign origin (i.e., not born in Sweden) of the mother and low parental education (Table 1). There was a weak correlation ($\rho = 0.239$, $P < 0.01$) between low maternal and low paternal education. The multivariate logistic regression model of the three psychosocial factors associated with increased concentrations of GADA included foreign origin of the mother (OR 2.1 [95% CI 1.3–3.3], $P < 0.001$) and low education of the father (1.6 [1.1–2.3], $P < 0.01$) as predictors.

The only psychological stress mechanism associated with double positivity was need for neonatal intensive care (Table 1).

The bivariate relations between diabetes-related autoantibodies on the one hand and potential confounds, such as diabetes heredity, increased parental age, early food introduction, size for gestational age, BMI at 1 year, child infections, and delivery mode, on the other were mainly nonsignificant (Table 1). However, more than two upper respiratory infections in the child during the 1st year of life was associated with high IA-2A con-

Table 1—Bivariate χ^2 associations to concentrations above the 95th percentile of IA-2A, GADA, and double positivity (n = 4,400)

| | IA-2A | | | | GADA | | | | Double positivity (i.e., IA-2A + GADA) | | | |
|---|-------------|-------------|----------|--------|-------------|-------------|----------|--------|---|-------------|----------|---------|
| | <95th (n/n) | >95th (n/n) | χ^2 | P | <95th (n/n) | >95th (n/n) | χ^2 | P | <95th (n/n) | >95th (n/n) | χ^2 | P |
| Psychological stress mechanisms | | | | | | | | | | | | |
| High parenting stress | 326/356 | 30/356 | 11.133 | <0.001 | — | — | — | NS | — | — | — | F NS |
| Lack of social support | — | — | — | NS | — | — | — | NS | — | — | — | F NS |
| Lack of confidence | — | — | — | NS | — | — | — | NS | — | — | — | F NS |
| Experiences of serious life events during 1st year of life | 157/172 | 15/172 | 5.988 | <0.05 | — | — | — | NS | — | — | — | F NS |
| Born abroad (mother) | — | — | — | NS | 227/250 | 23/250 | 9.616 | <0.01 | — | — | — | F NS |
| Born abroad (father) | — | — | — | NS | — | — | — | NS | — | — | — | F NS |
| Single parenthood | — | — | — | NS | — | — | — | NS | — | — | — | F NS |
| Low education (mother) | — | — | — | NS | 290/313 | 23/313 | 3.909 | <0.05 | — | — | — | F NS |
| Low education (father) | — | — | — | NS | 486/525 | 39/525 | 7.323 | <0.01 | — | — | — | F NS |
| Unemployed (mother) | 198/215 | 17/215 | 4.743 | <0.05 | — | — | — | NS | — | — | — | F NS |
| Unemployed (father) | — | — | — | NS | — | — | — | NS | — | — | — | F NS |
| Need for neonatal intensive care | — | — | — | NS | — | — | — | NS | 436/443 | 7/443 | — | F <0.05 |
| Potential confounding factors | | | | | | | | | | | | |
| Autoimmunity in the family | — | — | — | NS | — | — | — | NS | — | — | — | F NS |
| Type 1 diabetes in the family | — | — | — | NS | — | — | — | NS | — | — | — | F NS |
| Increased age (mother >30 years) | — | — | — | NS | — | — | — | NS | — | — | — | — |
| Increased age (father >30 years) | — | — | — | NS | — | — | — | NS | — | — | — | — |
| Exclusive breast-feeding (number of months) | — | — | — | M-W NS | — | — | — | M-W NS | — | — | — | M-W NS |
| Size for gestational age* | — | — | — | NS | — | — | — | NS | — | — | — | — |
| BMI at 1 year of age (>90th percentile) | — | — | — | NS | — | — | — | NS | — | — | — | F NS |
| Gastroenteritis (≥ 3 times) in the child during 1st year of life | — | — | — | NS | — | — | — | NS | — | — | — | F NS |
| Infections treated with penicillin (≥ 3 times) in the child during 1st year of life | — | — | — | NS | — | — | — | NS | — | — | — | F NS |
| Upper respiratory infection (≥ 2 times) in the child during 1st year of life | 453/488 | 35/488 | 5.820 | <0.05 | — | — | — | NS | 480/488 | 8/488 | — | F <0.05 |
| Cesarean section | — | — | — | NS | — | — | — | NS | — | — | — | F NS |

*Calculation of χ^2 for double positivity was not possible because of the small number in >25% of the cells. F, Fisher's exact test; M-W, Mann-Whitney test.

centrations. When this variable was included in the logistic regression analyses, the IA-2A model included experiences of a serious life event (OR 2.3 [95% CI 1.3–4.0], $P < 0.01$) and parenting stress (1.8 [1.2–2.9], $P < 0.01$). The P value for upper respiratory infections (1.6 [1.1–2.3]) was <0.05 ; therefore it was disregarded as a predictor due to the correction for multiple analyses.

There were no significant associations between psychosocial factors and enhanced immune responsiveness reflected as IgG-class antibodies toward tetanus toxoid. Furthermore, neither IA-2A ($\rho = 0.038$, NS) nor GADA ($\rho = 0.046$, NS) were correlated with antibodies toward tetanus toxoid.

CONCLUSIONS— In our prospective, population-based sample, we found high parenting stress, experiences of serious life events, foreign origin of the mother, and low socioeconomic status to be associated with β -cell–related autoimmunity in young children. These associations were found despite a slight underrepresentation of foreign origin and low education in the current sample. The above-mentioned psychosocial factors are well known in the literature as creating stress and strain in families, which in turn may stress the infants (14), probably because of their sensitivity to parental moods, signals, and behaviors (13). For example, parenting stress has been associated with poor marital quality (18), poor parental well being (18), and more caretaking hassles (19), i.e., poor infant sleep, feeding difficulties, excessive crying, colic, and childhood infections. Experiences of serious life events (e.g., parental separation, serious illness, or death in the family) has been suggested to trigger type 1 diabetes (8) or the autoimmune process behind the disease (9). Finally, to give birth to a child outside one's own native country might be perceived as extra-stressful, since becoming a parent is a major life transition that normally awakens thoughts about one's own origin and sometimes also a need for proximity to one's own parents.

The fact that need for neonatal intensive care was associated with double positivity, whereas neither size for gestational age nor BMI at 1 year were associated with diabetes-related autoimmunity, is interesting. Many infants who need intensive care have a low birth weight or are small

for date, with expected rapid weight gain, which according to the accelerator hypothesis is a risk for type 1 diabetes (5). However, treatment at a neonatal intensive ward includes daily repeated stressful and painful procedures, giving an extensive cortisol production in many children (20). Thus, treatment at a neonatal intensive ward could be interpreted as severe psychological stress, and one could speculate about the risk of insulin resistance and β -cell stress. It would indeed have been interesting to investigate the effect of early weight gain as well, but that could unfortunately not be assessed in the current study.

A number of potential confounding factors were investigated, but only repeated upper respiratory infections were significantly associated with diabetes-related autoantibodies in the initial univariate analyses. However, upper respiratory infections were not included among the predictors when included in the multivariate analysis.

Our results support the view that psychosocial stress in the family induces stress in the child (14) that is severe enough to trigger or promote the progression of β -cell–related autoimmunity in infants. There are a number of ways in which psychological stress may affect the body, e.g., via increased cortisol as well as catecholamine concentrations (11,21). Recently, stress has been associated with the development of allergies (22) and has been shown to influence the functional profile of T-cells (22–24). Furthermore, stress has been shown to modify the outcome of immunization in humans (25). We could not find any association between antibody levels of tetanus toxoid and stress factors. This may suggest that stress, in our study, specifically affected β -cell autoimmunity. In the case of diabetes-related autoimmunity, the link could be an increased need for insulin due to hyperglycemia or decreased insulin sensitivity caused by an upregulation of cortisol and catecholamine levels (14,21,26), placing increased demands on the insulin-producing β -cells (β -cell stress). However, measurement of insulin levels was not included in the ABIS protocol, and since whole-blood samples (taken at random and not after fasting) were collected, we were not able to perform the analyses. Thus, the mechanisms of how stress may induce β -cell autoimmunity remain unsolved in this early report of

psychological impact on β -cell autoimmunity.

In children with concentrations IA-2A or GADA above the 95th percentile, the occurrence of double positivity was found in ~15%, which indicates that these two autoantibodies are associated, though weakly, in the general population. It seems that IA-2A and GADA are induced independently in most children, and the trigger mechanisms of these two β -cell autoantibodies may be at least partly different. This view is also supported by studies showing genetic, age, and sex-related differences in the occurrence of β -cell autoantibodies (2). However, we considered serious life events, parenting stress, foreign origin, low education, and neonatal intensive care as markers of stress because they affect the family climate in a negative way, which in turn might induce stress in the child. Thus, the association found is between stress and β -cell autoimmunity (of which IA-2A and GADA are markers). Therefore, we have no explanation as to why associations with different psychological stress mechanisms were seen in relation to IA-2A, GADA, and double positivity. IA-2A is closely related to the risk of type 1 diabetes in children, whereas GADA is predictive of autoimmune diabetes in adolescents and adults. Insulin autoantibodies often appear as the first sign of β -cell autoimmunity in children and are associated with type 1 diabetes, especially in young children. In the current study, β -cell autoantibodies were studied in lysed capillary blood samples for which the analyses of insulin autoantibodies is not recommended due to high unspecific binding (data not shown). Thus, our results are restricted to the emergence of IA-2A and GADA.

High concentrations of IA-2A and GADA are the best markers for the development of type 1 diabetes (2). However, the levels of these autoantibodies fluctuate in early childhood (2). The occurrence of β -cell autoantibodies, either IA-2A or GADA, at 1 year of age does not imply a high risk of type 1 diabetes, and most of these infants will probably never develop the manifest disease. Thus, our results so far only imply that psychosocial stress is associated with the induction or progression of β -cell autoimmunity during the 1st year of life. The final aim is to study the importance of stress factors for the development of type 1 diabetes or decreased

glucose tolerance, but for this purpose a longer follow-up time is needed when an unselected population of children is studied prospectively.

In conclusion, we suggest that psychological stress, measured as psychosocial strain in families, might be involved in the induction or progression of diabetes-related autoimmunity in infants, possibly via β -cell stress. The findings of the current study give some support for a β -cell stress hypothesis as an extension of the accelerator hypothesis (5), in so far that a number of different factors, e.g., psychological stress, puberty, and rapid growth could be involved in the development of type 1 diabetes.

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