*RJDNMD*, **18**(4):313-323 *http://www.jrdiabet.ro*

# FEEDING, BIRTH WEIGHT AND RANK INFLUENCE ON THE RISK OF DIABETES MELLITUS IN CHILDREN

***Maricela Cobuz*** [1,✉], ***Claudiu Cobuz*** [2], ***Gabriela Creţeanu*** [2], ***Laura Bozomitu*** [1], ***Dan Moraru*** [1]

[1] "Gr.T.Popa" University of Medicine and Pharmacy of Iasi
[2] Center of Diabetes, Nutrition and Metabolic Diseases Suceava

*received*: October 10, 2011 *accepted*: November 11, 2011

*available online*: December 15, 2011

## Abstract

***Background:*** *The etiology of type 1 diabetes mellitus supposes the existence of genetic factors, but also environmental ones, of nutritional, fetal (e.g. birth weight) perinatal nature. This study aims at identifying food, rank and birth weight impact on the risk of developing this trouble.* ***Material and method:*** *192 children suffering from type 1 diabetes mellitus registered in the Centers for Diabetes, Nutrition and Metabolic Diseases of Iaşi and Suceava have been included in the study. We used anamnesis data regarding birth weight, birth rank, feeding type in the first months of life, in order to establish the risk of developing type 1 diabetes mellitus. The statistic processing has been performed by means of SPSS 17 specialized program.* ***Results:*** *There is a significant connection between the type of food and diabetes mellitus: the risk of developing diabetes mellitus is 4.45 times (RR=4.45) higher in the babies fed with milk formulae compared to the ones fed with breast milk. Breast-feeding duration was significantly shorter in the babies with diabetes mellitus (4 months ± 1.76 DS) compared to breast-feeding duration in babies belonging to the control group (6.56 months ± 2.74 DS). With respect to the birth weight, we can notice significantly high statistical values for the group of babies suffering from diabetes mellitus. The distribution of birth weight frequencies has the normal form of Gaussian curve, but with the extension of the right extremity, corresponding to LGA. With respect to birth rank, we can notice a predominance of the first and second child, however without a statistical significance.* ***Conclusions:*** *The multivariate analysis allows us to create a* risk profile *of the child with diabetes mellitus: the high birth weight determines a risk 2.17 times higher, the artificial feeding, a risk 4.35 times higher of developing diabetes mellitus, while the long breast-feeding duration shows a protective factor. The correct identification and the modification of these risk factors represent methods in which a large number of new cases of diabetes mellitus in babies can be prevented.*

***key words****: diabetes mellitus in children, feeding, birth weight, birth rank*

## Background

The etiology of type 1 diabetes mellitus is characterized by the destruction of $\beta$ pancreatic cells, because of an autoimmune process mediated by T lymphocytes, with an asymptomatic pre-diabetes phase. The autoimmune reaction occurs in predisposed subjects, under the influence of certain

✉ 16 University Street, Iasi, Romania; *corresponding author e-mail: maricelacobuz@yahoo.com*

activating or promoter environmental factors [1]. The genetic predisposition is suggested by the high recurrent risk among the relatives of patients with type 1 diabetes mellitus, and the genetic risk is established by HLA genotype [2]. Environmental factors' role in diabetes mellitus etiology is suggested by the low correspondence of the monozygotic twins [3], the geographical variation of the incidence of type 1 diabetes mellitus [4,5], prevalence's continuous increase [5,6].

The environmental factors having a role in the appearance of type 1 diabetes mellitus are of nutritional, fetal (e.g.: birth weight), perinatal nature [7]. In particular, among the nutritional factors, a short natural feeding period, followed by the early introduction of milk formulae was associated with a high risk of developing diabetes mellitus, in the epidemiologic studies [8,9]. The studies regarding auto-antibodies' appearance in type 1 diabetes mellitus proved that insular antigens appear around the age of 3-5 years, even if the disease appears at adult age [10].

The studies regarding birth rank provided inconstant results [11]. A larger number of brothers, so an increase of birth rank is associated with a low risk of type 1 diabetes mellitus [12,13].

As in the case of type 2 diabetes mellitus, prenatal and postnatal factors with early action can influence in a decisive manner the risk of developing type 1 diabetes mellitus. They also include birth weight, together with the intrauterine exposure to viral infections. Birth weight is one of the most accessible epidemiologic variables. Infant's weight is strongly associated with the mortality risk in the first year of life and with the one of morbidities' appearance in childhood and then, in the adulthood.

In the context of these characteristics of environmental factors' influence in type 1 diabetes mellitus etiopathology, this study aims at identifying feeding, birth rank and weight impact on the risk of this disease.

**Material and method**

192 children suffering from type 1 diabetes mellitus, registered in the Centers for Diabetes, Nutrition and Metabolic Diseases of Iaşi and Suceava have been included in the study. The patients have been assessed according to birth weight, birth rank, type of feeding in the first months of life in order to establish the risk of developing type 1 diabetes mellitus. Anamnesis data has been used; diabetes mellitus type one being defined according to ADA criteria. The statistical analysis included parametric and non-parametric tests, mathematical methods implemented in the soft used for data (Statistics) dedicated to the medical research, methods allowing the calculation of certain statistic markers specific to the type of data, prevision (prognosis) methods. The statistical processing has been performed by means of SPSS 17 specialized program.

**Results**

For risk factors analysis in diabetes mellitus appearance, two children groups have been used, the first one representing the study group – children with diabetes mellitus (N=192), and the second representing the control group – children without diabetes mellitus (N=30). From the point of view of the epidemiological data, the two groups were homogenous, being represented by 56.67% male children in the control group and 43.33% in the study group, respectively 43.3% female children in the control group and 47.92% in the study group.

Certain epidemiological studies describe the fact that the short natural feeding period, followed by the early introduction of milk formulae is one of the nutritional factors. This aspect is also noticed in the present study, where we can see an increase of prevalence of the number of cases diagnosed with diabetes mellitus once with the appearance of milk formulae.

If in 1990 there were only 1.04% babies with diabetes mellitus, in the study group their percent increased significantly starting from the year 1994 (10.94%), and after 2000 we can notice a significant decrease, which can be explained on the one hand by the qualitative improvement of milk formulae and on the other hand by the promotion of breast milk importance as an essential food for the infant (Figure 1, Table 1).

**Table 1.** Cases distribution according to age in the study group.

| 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 4 | 4 | 5 | 21 | 16 | 16 | 21 | 13 | 18 | 16 | 10 | 11 | 10 | 4 | 8 | 5 | 3 | 3 | 2 |
| 1.04% | 2.08% | 2.08% | 2.60% | 10.94% | 8.33% | 8.33% | 10.94% | 6.77% | 9.38% | 8.33% | 5.21% | 5.73% | 5.21% | 2.08% | 4.17% | 2.60% | 1.56% | 1.56% | 1.04% |

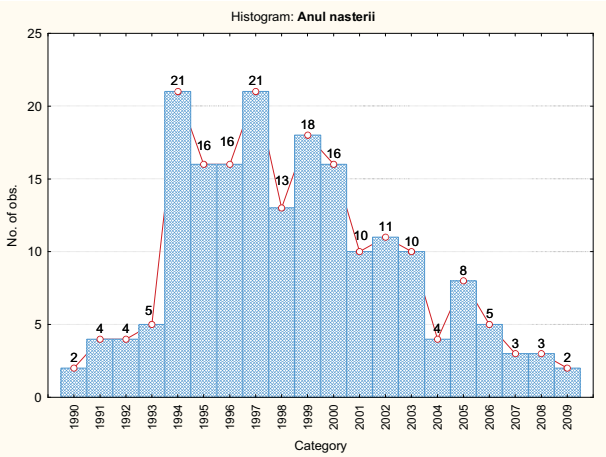


**Fig. 1.** Connection between the year of birth and diabetes mellitus appearance.

**Table 2.** Cases distribution according to feeding type vs. study group (diabetes mellitus/control group).

| | Feeding type | | Total |
|---|---|---|---|
| | Milk Formula | Breast Milk | |
| Control Group | 5 | 25 | 30 |
| | 16.67% | 83.33% | |
| Study Group (DM) | 142 | 50 | 192 |
| | 73.96% | 26.04% | |
| Total | 147 | 75 | 222 |

Cases distribution according to feeding type and diabetes mellitus presence highlights the fact that 73.96% of the babies in the study group have been fed with milk formulae, while the frequency of babies fed with milk formulae in the control group was of 16.67% only. (Table 2, Figure 2)

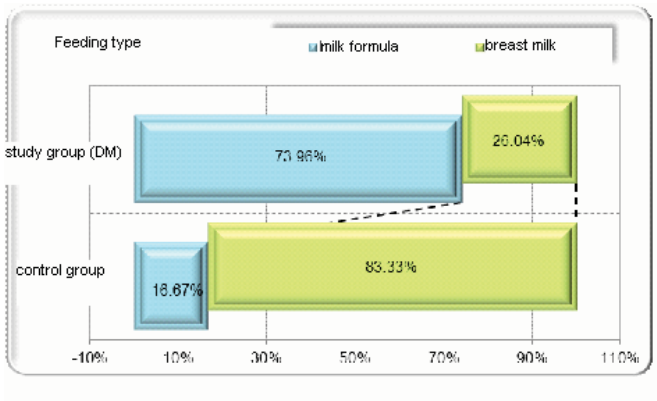


**Fig. 2.** Connection between feeding in the first months of life – diabetes mellitus.

There is a significant association between the feeding type and the presence of diabetes mellitus in children, aspect which has been demonstrated in the study group by the results of the non-parametric analysis ($\chi^2$=38.06, p<<0.05, 90%CI).

The risk of diabetes mellitus appearance is 4.45 times (RR=4.45) higher in babies fed with milk formulae compared with the ones fed with breast milk (Table 3).

**Table 3.** Assessment of opportunity and risk parameters in the appearance of diabetes mellitus caused by the feeding with milk formulae.

| | Assessed value | *95% Confidence interval* | |
|---|---|---|---|
| | | Minimum | Maximum |
| Opportunity PARAMETERS | | | |
| Opportunity Ratio (OR) | 14.2 | 4.81 | 44.94 |
| Risk PARAMETERS | | | |
| Risk Ratio (RR) | 4.45 | 1.23 | 6.71 |

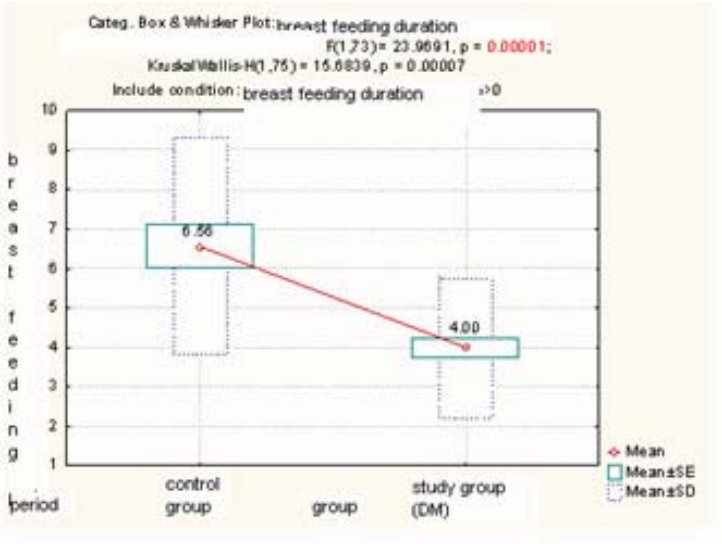


**Fig. 3.** Average value of breast feeding duration vs. diabetes mellitus.

Analyzing only breast-fed babies, the study highlighted a significantly shorter breast feeding duration (F=15.68, p=0.00007, 95%CI) in children with diabetes mellitus (4 months±1.76 DS) compared with the breast feeding duration of the children belonging to the control group (6.56 months±2.74 DS). (figure 3)

With respect to the birth weight, we can notice high values for the group of children with diabetes mellitus (figure 4).

The results of the comparative analysis of birth weight of children belonging to the two analyzed groups have been obtained by applying Kruskal-Wallis test, a very robust non-parametrical test, based on ranks' analysis. The two subgroups studied (DM group vs. control group) have been represented by samples with unequal dimensions and different variances (Levene Test – F=13.298, p=0.000332), these aspects determining the implementation of a non-parametrical test (Table 4).

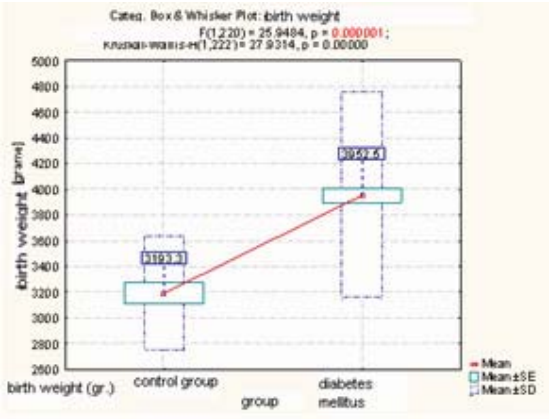


**Fig. 4.** Average value of birth weight vs. diabetes mellitus

**Table 4.** Test for comparing birth weights average values vs. diabetes mellitus.

| | F *(95% confidence interval)* | p |
|---|---|---|
| Kruskal-Wallis Test | 25.94845 | 0.000001 |

**Table 5.** Cases distribution according to birth weight vs. diabetes mellitus.

| | Classification – birth weight | | | Total |
|---|---|---|---|---|
| | LGA | AGA | SGA | |
| Control group | 2 | 27 | 1 | 30 |
| | 6.67% | 90.00% | 3.33% | |
| Study group (DM) | 79 | 108 | 5 | 192 |
| | 41.15% | 56.25% | 2.60% | |
| Total | 81 | 135 | 6 | 222 |

To sum up, there are significant statistical differences (F=25.946, p<<0.01, 95% CI) between the birth weight of the children with diabetes mellitus and the one of the children belonging to the control group.

In order to describe birth weight influence in relation to the gestational age on the risk of diabetes mellitus appearance, we have used the following classification:

– Large for Gestational Age (LGA) (> percentile 90)
– Appropriate for Gestational Age (AGA) (between percentile 10 and 90)
– Small for Gestational Age (SGA) (< percentile 10)

Cases distribution according to birth weight in the study group was the following (Table 5, Figure 5):

We can notice the high frequency of children with higher birth weight than the one appropriate for the gestational age.

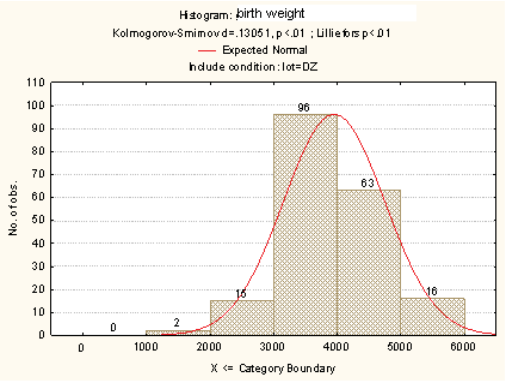


**Fig. 5.** Histogram of birth weight values in children with diabetes mellitus.

The distribution of birth weight frequencies has the normal form of Gaussian curve, but with the extension of the right extremity, corresponding to LGA. Compared with the control group, we can notice a significant statistical difference corresponding to LGA category. (Figure 6, Table 6)

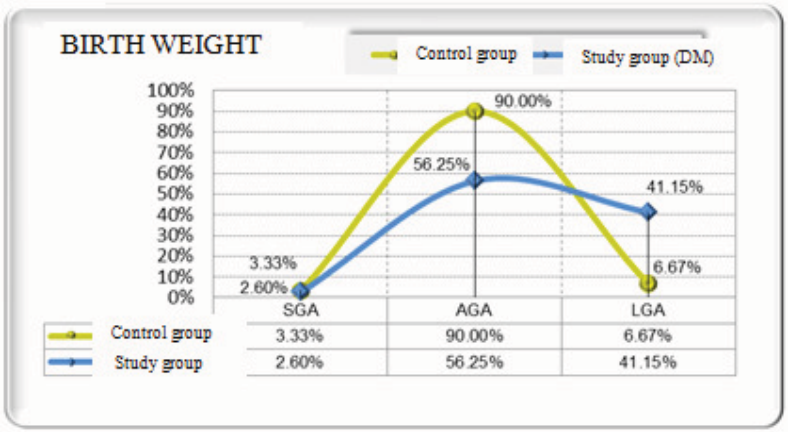


**Fig. 6.** Cases distribution according to birth weight vs. diabetes mellitus.

**Table 6.** Assessed parameters in testing the connection between birth weight and diabetes mellitus.

| df=2 | Chi-square $\chi^2$ | P<br>*95% confidence interval* |
|---|---|---|
| Pearson Chi-square- $\chi^2$ | 13.36482 | 0.00125 |
| M-L Chi-square | 16.56789 | 0.00025 |
| Correlation coefficient (Spearman Rank R) | 0.6993659 | 0.00069 |

With regard to birth rank, we can notice a predominance of the first and second child. (Table 7, Figure 7). The statistical processing has not proved a significant relationship from a statistical point of view, but the multivariate analysis has identified a certain protective effect, obtained by the increase of birth rank.

**Table 7.** Cases distribution according to birth rank vs. diabetes mellitus.

| | rank - 1 | rank - 2 | rank - 3 | rank - 4 | rank - 5 | rank - 6 | Total |
|---|---|---|---|---|---|---|---|
| Control group | 8 | 12 | 7 | 2 | 1 | 0 | 30 |
| | 26.67% | 40.00% | 23.33% | 6.67% | 3.33% | 0.00% | |
| Study group (DM) | 97 | 58 | 20 | 12 | 4 | 1 | 192 |
| | 50.52% | 30.21% | 10.42% | 6.25% | 2.08% | 0.52% | |
| Total | 105 | 70 | 27 | 14 | 5 | 1 | 222 |

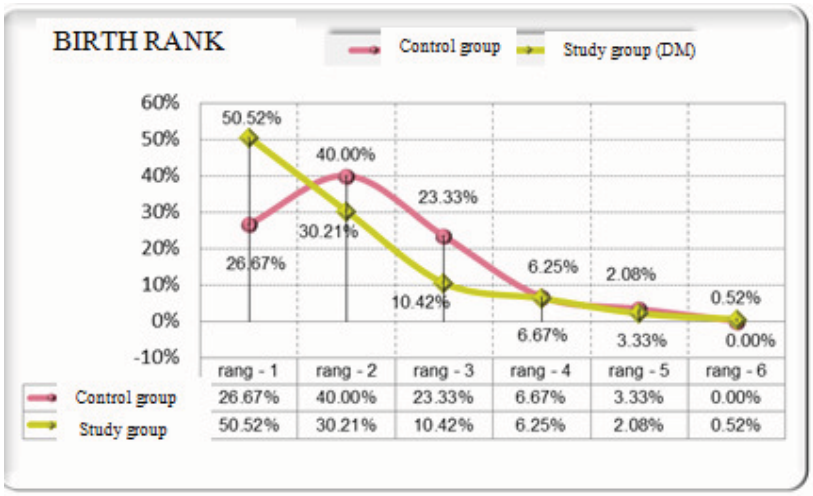


**Fig. 7.** Cases distribution according to birth rank vs. diabetes mellitus.

**Multivariate analysis of risk factors**

Having in view the studied nutritional, fetal and perinatal factors, we aim at realizing a *risk profile* of the child with diabetes mellitus. (Table 8)

**Table 8.** Multiple correlation of DM presence vs. risk factors.

| Partial correlation | Correlation coefficient (Beta) | Std.Err. (Beta) | B | Std.Err. B | t | p<br>*95% confidence interval* |
|---|---|---|---|---|---|---|
| Intercept | | | 0.671173 | 0.120207 | 5.58349 | 0.000000 |
| Birth weight | 0.478231 | 0.064254 | 0.000076 | 0.000027 | 2.77383 | 0.006023 |
| Birth rank | -0.039592 | 0.056195 | -0.012893 | 0.018300 | -0.70455 | 0.481844 |
| Feeding type | 0.542543 | 0.112431 | 0.256057 | 0.081266 | 3.15087 | 0.001857 |
| Breast-feeding duration | -0.780676 | 0.104383 | -0.099053 | 0.013244 | -7.47892 | 0.000000 |

The table contains predictive risk factors for the appearance of diabetes mellitus in children. Based on the results, we can appreciate the fact that breast-feeding duration (r=-0.78, p<<0.01), feeding type (r=0.54, p=0.0018) and birth weight (r=0.47, p=0.0060) are significant predictive risk

factors for diabetes mellitus appearance (Table 8).

The multivariate analysis' results are presented in a suggestive manner in the following chart (fig. 8). The low value of the signification level in the case of *intercept* variable shows the fact that diabetes mellitus appearance is also influenced by other factors which are not present in this analysis.

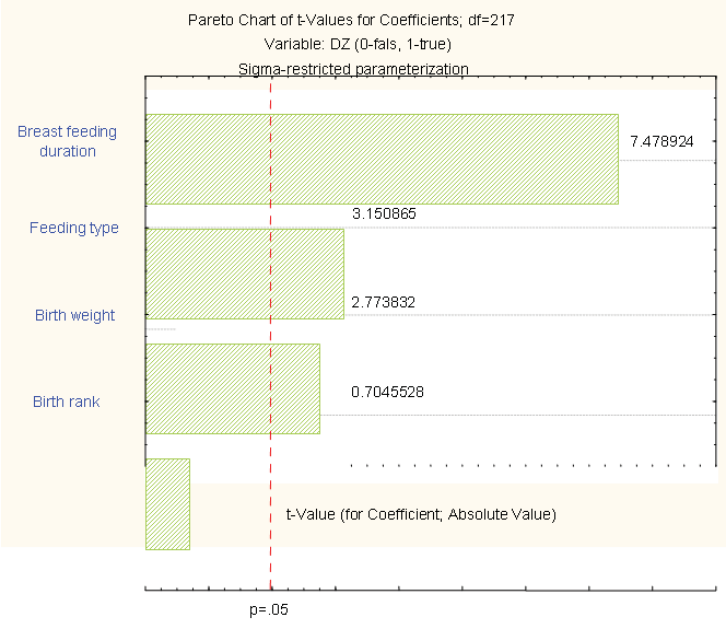


**Fig. 8.** Absolute value of "t" statistics in assessing the multivariate analysis.

**Table 9.** Generalized regression model – risk ratio of the predictive factors in DM.

| | p<br>95%CI | Beta (ß)<br>Risk ratio | St.Err.ß | -95.00%<br>- Cnf.Lmt | +95.00%<br>- Cnf.Lmt |
|---|---|---|---|---|---|
| Intercept | 0.000000 | | | | |
| Birth weight | 0.006023 | 2.178231 | 0.064254 | 1.051588 | 6.304874 |
| Birth rank | 0.481844 | -0.039592 | 0.056195 | -0.150350 | 0.071165 |
| Feeding type | 0.001857 | 4.354254 | 0.112431 | 2.132658 | 7.575851 |
| Breast-feeding duration | 0.000000 | -5.780676 | 0.104383 | -3.986412 | -11.574941 |

Applying the generalized regression model, we can assess the risk ratio of each factor considered in the predictive analysis according to the following table, where $\beta$ values show the risk ratio of each analyzed variable (Table 9).

To sum up, the most important risk factor is the feeding type (breast milk vs. milk formula) (RR=4.35) and breast-feeding duration (RR=5.7).

**Discussions**

The appearance of diabetes mellitus in children depends on the presence of environmental factors. Infant diet can influence the risk of developing type 1 diabetes mellitus, by activating the autoimmune process at the level of the insufficiently matured intestinal immune system, with the production of certain cross reactions antigen-antibodies [14]. Diet's aspects can determine the increase of diabetes mellitus risk by other metabolic means,

recently described: *accelerator hypothesis* or *overload hypothesis* (by birth weight increase, growth acceleration and rapid weight gain) [15], because breast-fed children presented a much slower postnatal growth, without presenting the risk of developing obesity [16]. One study only proved that the early introduction of artificial feeding and an accelerated growth rhythm represent *independent risk factors* for the appearance of diabetes mellitus [17].

The data presented in our study prove an inverse relationship between breast-feeding and the risk of developing diabetes mellitus. Recent prospective studies highlighted a relationship between ß – cellular autoimmunity increase and the early introduction of cereals [18,19]. The obtained results highlight breast-feeding protective role for diabetes mellitus appearance.

The studies regarding the association between birth weight and the risk of developing type 1 diabetes mellitus are contradictory. Some of them proved a high risk in the infants with high birth weight and a low risk for the infants with low weight [20,21,22]. The relationship between diabetes mellitus and high birth weight was almost linear. Other studies have noticed a connection between the low birth weight and diabetes mellitus [23,24].

The data collected prove a significantly statistical relationship between the high birth weight and the risk of developing diabetes mellitus. The excess of adipose tissue can determine insulin resistance appearance in childhood, according with the overload theory [14]. Moreover, we can notice an increase in the birth weight in developed countries, in accordance with the fast increase in the incidence of type 1 diabetes mellitus [25,26]. The birth weight influences the risk of developing type 1 diabetes mellitus, but possibly in association with other specific genotypes, which also offer a high risk (HLA-DQ8/DQ2) [27,28]. Therefore, the risk genotype can influence in a decisive manner the risk of type 1 diabetes mellitus, by the physic-pathological means mentioned above.

The connection between birth rank and the risk of developing type 1 diabetes mellitus is inconclusive. The statistical processing proved an inverse relation, but with low power. The multivariate analysis proved a certain protective effect of the higher birth rank. *Hygiene hypothesis* supposes early infections which determine the maturation of the immune system [29]. Attending the community, potentially associated with a risk of intercurrent infections, can represent a protective factor for the appearance of type 1 diabetes mellitus, as it appears in a recent meta analysis, comprising children younger than 4 years [30]. A large family could not mediate the similar protection mechanisms. Therefore, the small number of children in the families from the developed countries in recent decades can contribute to the incidence increase of type 1 diabetes mellitus. However, in this study, the inverse association between family's size or birth rank and the risk of developing type 1 diabetes mellitus was not supported.

**Conclusions**

The multivariate analysis of nutritional, fetal and perinatal risk factors allows us to make a *risk profile* of the child with diabetes mellitus: breast-feeding duration, the type of feeding and birth weight are significant predictive risk factors for diabetes mellitus appearance. Therefore, the high birth weight

determines a risk 2.17 times higher, the artificial feeding, a risk 4.35 times higher for diabetes mellitus appearance, while the long breast-feeding duration shows a protective factor.

These observations which assess the simultaneous presence of these risk factors can explain the increased incidence of diabetes mellitus in children. Moreover, their correct identification and modification are means by which a large number of new cases of diabetes mellitus can be prevented.

## REFERENCES


**1. Atkinson MA, Eisenbarth GS.** Type 1 diabetes: new perspectives on disease pathogenesis and treatment. *Lancet* 2001; 358:221–229.

**2. Gillespie KM, Gale EA, Bingley PJ.** High familial risk and geneticsusceptibility in early onset childhood diabetes. *Diabetes* 2002; 51: 210–214.

**3. Kumar D, Gemayel NS, Deapen D, *et al.*** North-American twins with IDDM. Genetic, etiological, and clinical significance of disease concordance according to age, zygosity, and the interval after diagnosis in first twin. *Diabetes* 1993; 42: 1351–1363.

**4. Karvonen M, Viik-Kajander M, Moltchanova E, Libman I, LaPorte R, Tuomilehto J.** Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group. *Diabetes Care* 2000; 23: 1516–1526.

**5. Green A, Patterson CC.** Trends in the incidence of childhoodonset diabetes in Europe 1989 1998. *Diabetologia* 2001; 44(Suppl. 3): B3–B8.

**6. Onkamo P, Vaananen S, Karvonen M, Tuomilehto J.** Worldwide increase in incidence of Type I diabetes–the analysis of the data on published incidence trends. *Diabetologia* 1999; 42: 1395–1403.

**7. Soltesz G.** Diabetes in the young: a paediatric and epidemiological perspective. *Diabetologia* 2003; 46: 447–454.

**8. McKinney PA, Parslow R, Gurney KA, Law GR, Bodansky HJ, Williams R.** Perinatal and neonatal determinants of childhood type 1 diabetes. A case-control study in Yorkshire, U.K. *Diabetes Care* 1999; 22: 928–932.

**9. Sipetic SB, Vlajinac HD, Kocev NI, Marinkovic JM, Radmanovic SZ, Bjekic MD.** The Belgrade childhood diabetes study: a multivariate analysis of risk determinants for diabetes. *Eur J Public Health* 2005; 15: 117–122.

**10. Ziegler AG, Hummel M, Schenker M, Bonifacio E.** Autoantibody appearance and risk for development of childhood diabetes in offspring of parents with type 1 diabetes. The 2-year analysis of the German BABYDIAB study. *Diabets* 1999;48:460-8.

**11. Patterson CC, Carson DJ, Hadden DR, Waugh NR, Cole SK.** A case-control investigation of perinatal risk factors for childhood IDDM in Northern Ireland and Scotland. *Diabetes Care* 1994;17:376–81

**12. Stene LC, Magnus P, Lie RT, Sovik O, Joner G.** Maternal and paternal age at delivery, birth order and risk of childhood onset type 1 diabetes: population based cohort study. *BMJ* 2001; 323:369.

**13. Wadsworth EJ, Shield JP, Hunt LP, Baum JD.** A case-control study of environmental factors associated with diabetes in the under 5s. *Diabet Med* 1997; 14: 390–396.

**14. Harrison LC, Honeyman MC.** Cow's milk and type 1 diabetes: the real debate is about mucosal immune function. *Diabetes* 1999; 48: 1501–1507

**15. Dahlquist G.** Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis. *Diabetologia* 2006; 49: 20–24.

**16. Owen CG, Martin RM, Whincup PH, Smith GD, Cook DG.** Effect of infant feeding on the risk of obesity across the life course: a quantitative review of published evidence. *Pediatrics* 2005; 115: 1367–1377

**17. Hypponen E, Kenward MG, Virtanen SM, et al.** Infant feeding, early weight gain and risk of type 1 diabetes. Childhood Diabetes in Finland (DiMe) Study Group. *Diabetes Care* 1999; 22: 1961–1965.

**18. Ziegler AG, Schmid S, Huber D, Hummel M, Bonifacio E.** Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. *JAMA* 2003; 290: 1721–1728.

**19. Norris JM, Barriga K, Klingensmith G, et al.** Timing of initial cereal exposure in infancy and risk of islet autoimmunity. *JAMA* 2003; 290: 1713–1720.

**20. Cardwell CR, Carson DJ, Patterson CC.** Parental age at delivery, birth order, birth weight and gestational age are associated with the risk of childhood Type 1 diabetes: a UK regional retrospective cohort study. *Diabet Med* 2005; 22: 200–206.

**21. Dahlquist GG, Patterson C, Soltesz G.** Perinatal risk factors for childhood type 1 diabetes in Europe. The EURODIAB Substudy 2 Study Group. *Diabetes Care* 1999; 22: 1698–1702.

**22. Stene LC, Magnus P, Lie RT, Sovik O, Joner G.** Birth weight and childhood onset type 1 diabetes: population based cohort study. *BMJ* 2001; 322: 889–892.

**23. Stene LC, Thorsby PM, Berg JP, Ronningen KS, Undlien DE, Joner G.** The relation between size at birth and risk of type 1 diabetes is not influenced by adjustment for the insulin gene (-23HphI) polymorphism or HLA-DQ genotype. *Diabetologia* 2006; 49: 2068–2073.

**24. Wei JN, Li HY, Chang CH, et al.** Birth weight and type 1 diabetes among schoolchildren in Taiwan–A population-based casecontrolled study. *Diabetes Res Clin Pract* 2006; 74: 309-315.

**25. Green A, Patterson CC.** Trends in the incidence of childhoodonset diabetes in Europe 1989–1998. *Diabetologia* 2001; 44(Suppl. 3): B3–B8

**26. Onkamo P, Vaananen S, Karvonen M, Tuomilehto J.** Worldwide increase in incidence of Type I diabetes–the analysis of the data on published incidence trends. *Diabetologia* 1999; 42: 1395–1403.

**27. Stene LC, Magnus P, Ronningen KS, Joner G.** Diabetesassociated HLA-DQ genes and birth weight. *Diabetes* 2001; 50: 2879–2882.

**28. Ong KK, Petry CJ, Barratt BJ, et al.** Maternal-fetal interactions and birth order influence insulin variable number of tandem repeats allele class associations with head size at birth and childhood weight gain. *Diabetes* 2004; 53: 1128–1133.

**29. McKinney PA, Okasha M, Parslow RC, et al.** Early social mixing and childhood Type 1 diabetes mellitus: a case- control study in Yorkshire, UK. *Diabet Med* 2000; 17: 236–242.

**30. Kaila B, Taback SP.** The effect of day care exposure on the risk of developing type 1 diabetes: a meta-analysis of case-control studies. *Diabetes Care* 2001; 24: 1353–1358.