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Metabolic syndrome in subjects at high risk for type 2 diabetes: The genetic, physiopathology and evolution of type 2 diabetes (GENFIEV) study

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KEYWORDS
Metabolic syndrome;
Insulin resistance;
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Abstract *Background and Aim:* We evaluated the relationship between insulin resistance (IR) and insulin secretion with the metabolic syndrome (MS) in 885 subjects (377 men/508 women, age 49 ± 11 years, BMI 29 ± 5.2 kg m^{-2}) at risk of diabetes enrolled in the genetics, pathophysiology and evolution of type 2 diabetes (GENFIEV) study.
Methods and Results: All subjects underwent a 75-g oral glucose tolerance test (OGTT) for the estimation of plasma levels of glucose and C-peptide, as well as fasting insulin and lipid profile. IR was arbitrarily defined as HOMA-IR value above the 75th centile of normal glucose tolerance (NGT) subjects. Overall MS prevalence (National Cholesterol Treatment Panel—Adult Treatment Panel (NCEP—ATPIII) criteria) was 33%, 19% in subjects with NGT, 42% in impaired fasting glucose (IFG), 34% in impaired glucose tolerance (IGT), 74% in IFG + IGT subjects, and 56% in newly diagnosed diabetic patients. Prevalence was slightly higher with IDF criteria. MS prevalence was >50% in subjects with 2 h glucose >7.8 mmol l^{-1}, independently of fasting plasma glucose. IR prevalence was higher in subjects with MS than in those without (63% vs. 23%; $p < 0.0001$) and increased from 54% to 73% and 88% in the presence of three, four or five traits, respectively. IR occurred in 42% of subjects with non-diabetic alterations of glucose homeostasis, being the highest in those with IFG + IGT (IFG + IGT 53%, IFG 45%, IGT 38%; $p < 0.0001$). Individuals with MS were more IR irrespective of glucose tolerance ($p < 0.0001$) with no difference in insulinogenic index. Hypertriglyceridaemia (OR: 3.38; Confidence Interval, CI: 2.294.99), abdominal obesity (3.26; CI: 2.18—4.89), hyperglycaemia (3.02; CI: 1.80—5.07) and hypertension (1.69; CI: 1.12—2.55) were all associated with IR.
Conclusions: These results show that in subjects with altered glucose tolerance (in particular IFG + IGT) MS prevalence is high and is generally associated to IR. Some combinations of traits of MS may significantly contribute to identify subjects with IR.

In addition to predicting cardiovascular disease (CVD), morbidity and mortality, the metabolic syndrome (MS) is strongly associated with the development of type 2 diabetes mellitus (T2DM), itself an important risk factor for CVD [1]. In patients with T2DM, MS is highly prevalent[2—5] and predicts both micro- and macrovascular complications [2,5]. Individuals with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) are at high risk of developing T2DM and CVD [6]. Approximately 70—75% of individuals with impaired glucose regulation (IGR: IFG, IFG + IGT and IGT) meet the criteria for MS [7,8]. The Botnia study showed that in patients with IGR, 64% of men and 42% of women had MS, while among NGT subjects, the prevalence of MS was 15% in men and 10% in women [9]. According to some investigators [9—11], pre-diabetes carries a predictive power for CVD similar to that of MS [9—11], but this predictive potential most likely can be explained by the accompanying metabolic risk factors [12].

Although the underlying pathophysiology of MS is still not fully understood, it is generally believed that insulin resistance (IR) plays a central role in its pathogenesis [13,14]. IR is closely linked to the risk of developing CVD [9,15]. Moreover, IR plays a major role in the pathophysiology of glucose intolerance and T2DM [13,14]. Although IR is a well-recognised risk factor for T2DM, it is also appreciated that the main mechanism responsible for the development of overt hyperglycaemia rests in the progressive loss of β-cell function. From this point of view, it is noteworthy that only few investigations have explored the deterioration of IR and β-cell function in individuals at high risk for T2DM with and without MS [16]. Therefore, we have analysed data collected from the genetics, pathophysiology and evolution of type 2 diabetes (GENFIEV) study recruiting subjects at high risk of T2DM to evaluate: (i) prevalence of MS, (ii) relative role of IR and insulin secretion, and (iii) cardiovascular risk profile associated with MS.

Methods

The GENFIEV study is a multicentre nationwide Italian study designed to recruit individuals with IFG and/or IGT in the attempt to identify phenotypic and genotypic features that may allow the identification of subjects at high risk for T2DM (http://clinicaltrials.gov/ct2/show/NCT00879801?term=GENFIEV&rank=1). To this purpose, an opportunistic recruitment was performed by screening individuals referred to diabetes clinics because of the potential risk of T2DM. Fourteen centres across Italy participated in the study. The study was approved by Institutional Review Boards, and all subjects gave written informed consent before entering the study.

A total of 1017 subjects have been recruited over a 3-year period (between 2003 and 2005). All subjects underwent a standardised medical history, physical examination, and laboratory testing and those with no known diagnosis of T2DM underwent a 75-g oral glucose tolerance test (OGTT). Height, weight and waist circumference (at the umbilicus with the subject standing) were measured, and BMI calculated as kg m^{-2}. Two blood pressure measurements were taken with a standard mercury sphygmomanometer with subjects on a recumbent position and the mean value was considered. A 12-lead standard electrocardiogram (ECG) was also recorded.

All OGTTs were performed after an overnight fasting with all subjects refraining from smoking for no less than 12 h before the test. In all subjects, an antecubital vein was cannulated for blood sample drawing. Plasma glucose, insulin and C-peptide levels as well as lipid profile were determined in fasting condition. All subjects ingested a 75 g

of glucose load over 5 min and samples were drawn at 15, 30, 60, 90 and 120 min for plasma glucose and C-peptide determinations.

All biochemical parameters were determined by standard methods on Roche-Modular Autoanalyzer (Milan, Italy). Insulin and C-peptide were determined centrally in the Pisa laboratory by immunoassay (Immulite, DPC; Los Angeles, CA, USA). LDL-cholesterol (LDL-C) was calculated according to the Friedewald formula. Based on OGTT, subjects were divided into five categories: normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), IFG + IGT and T2DM according to the American Diabetes Association 1997 criteria [17]. The MS was diagnosed according to the National Cholesterol Education Program—Adult Treatment Panel (NCEP—ATP) III [18], International Diabetic Federation (IDF) [19] and the more recent International Diabetic Federation/American Heart Association/National Heart, Lung and Blood Institute (IDF/AHA/NHLBI) criteria [20]. The NCEPT—ATPIII definition has been used for data analysis, unless specified differently. HOMA-IR index was calculated (fasting insulin ($mU\,l^{-1}$) × fasting plasma glucose ($mmol\,l^{-1}$)/22.5) as described by Matthews et al. [21]. IR was arbitrarily defined as HOMA-IR value above the 75th centile of NGT subjects. The insulinogenic index was calculated as $CP_{30} - CP_0/18 \times (G_{30} - G_0)$, where CP_0 and G_0 are the fasting plasma levels of plasma C-peptide and glucose, respectively, and CP_{30} and G_{30} their levels at 30 min [22]. Beta-cell performance (disposition index) was calculated as the insulinogenic index/HOMA-IR ratio.

All statistical analyses were performed using the StatView software (SAS Institute; Cary, NC, USA) on Power Mac G5 (Apple; Cupertino, CA, USA). Data are expressed as mean ± SD. Non-parametric statistic analysis was performed to compare categorical variable among groups. Analysis of variance (ANOVA) was employed to test mean differences among groups, whereas multiple logistic regression was used to test the association of MS traits and IR. Results from this analysis are presented as odds ratio (OR) with 95% confidence intervals (CI). p values <0.05 were considered statistically significant.

Results

A total of 885 subjects (377 men/508 women, age 49 ± 11 years, BMI 29 ± 5.2 $kg\,m^{-2}$) were evaluated in this study. Based on the OGTT results, 53% had NGT, 4% IFG, 25% IGT, 8% both IFG and IGT and 10% were diagnosed with T2DM. An additional 5% of the subjects had FPG diagnostic for T2DM.

With MS diagnosed based on NCEP—ATPIII criteria, hypertension was the most common trait (63%), followed by obesity (58%), low HDL-cholesterol (34%) and high triglycerides (33%), while hyperglycaemia was the least frequent component (21%). The prevalence of MS was 33% (37% in men and 30% in women, $p < 0.0001$) and increased from 19% in NGT to 42% in those with IFG, 34% in those with IGT, 74% in IFG + IGT subjects and 56% in newly diagnosed T2DM patients (Fig. 1). There was no difference in the MS prevalence among NGT, IGR or T2DM male versus female subjects.

To ascertain whether different definitions may yield different prevalence, MS was diagnosed also on the basis of both IDF criteria and the new IDF/AHA/NHLBI definition. As shown in Fig. 1, IDF and IDF/AHA/NHLBI definitions tended to give slightly higher overall prevalence of the MS (36.5% with IDF and 38.2% with IDF/AHA/NHLBI) raising from 22.5% and 23.5% in NGT to 59% and 61.3% in those with IFG, 40% and 41% in IGT, 79% and 86.8% in IFG + IGT, and 60% and 62.5% in T2DM, respectively.

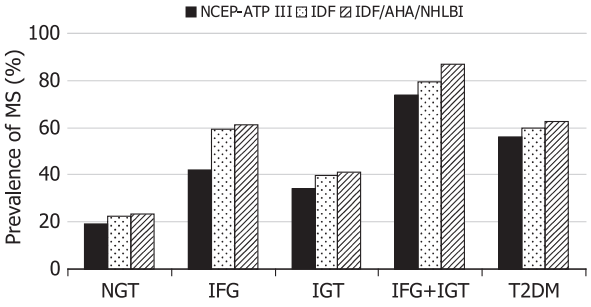

Figure 1 Prevalence of metabolic syndrome (MS) among categories of glucose regulation, according with different MS definitions.

The clinical and biochemical features of subjects with and without MS are given in Table 1, while Fig. 2 illustrates the prevalence of the MS, according to glucose tolerance and fasting plasma glucose (FPG) levels. This analysis highlights the effect of 2-h OGTT glucose on the prevalence of MS, irrespective of FPG. Thus, with an FPG not diagnostic for the MS ($<5.6\,mmol\,l^{-1}$), its prevalence increased from 19% in NGT to 35% in IGT ($p < 0.0001$) and 33% in T2DM groups, respectively. Similarly, in subjects with IFG (FPG: 5.6—6.1 $mmol\,l^{-1}$), the MS prevalence increased from 44% in NGT to 67% in IGT and 69% in T2DM.

Fasting plasma insulin and C-peptide concentrations were higher in subjects with MS with the exception of IFG

Table 1 Clinical and biochemical features of subjects with and without MS included in the study.

	MS+	MS−	p
Subjects (%)	292 (33)	593 (67)	
Age (years)	60 ± 10	46 ± 12	<0.0001
Waist (cm)	109 ± 11	97 ± 14	<0.0001
BMI (kg/m^2)	32 ± 5	28 ± 5	<0.0001
Systolic blood pressure (mmHg)	136 ± 15	125 ± 14	<0.0001
Diastolic blood pressure (mmHg)	87 ± 10	79 ± 10	<0.0001
Glycemia (mmol/l)	5.72 ± 0.78	5.33 ± 0.78	<0.0001
Total-C (mmol/l)	5.49 ± 0.96	5.36 ± 1.06	ns
LDL-C (mmol/l)	3.57 ± 0.90	3.42 ± 0.96	<0.05
HDL-C (mmol/l)	1.14 ± 0.26	1.48 ± 0.36	<0.0001
Triglycerides (mmol/l)[a]	2.01 (1.16)	1.08 (0.63)	<0.0001
Fasting plasma insulin (μU/ml)	16.2 ± 9.6	10.2 ± 6.2	<0.0001
Fasting plasma C-peptide (ng/ml)	3.0 ± 1.2	2.1 ± 0.9	<0.0001
HOMA-IR	4.04 ± 2.8	2.27 ± 1.38	<0.0001

[a] Median (IQR).

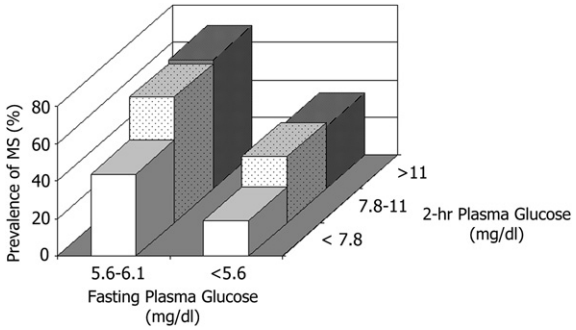

Figure 2 Prevalence of metabolic syndrome (MS) stratified by fasting plasma glucose (FPG) and 2-hplasma glucose (2-h PG).

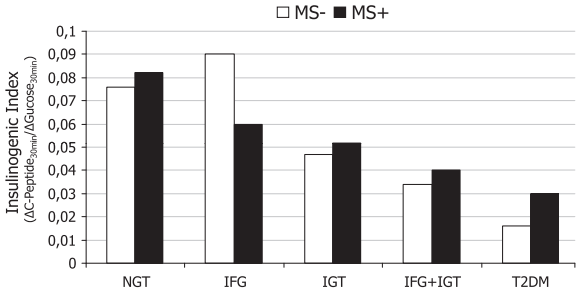

Figure 4 Insulinogenic index according to the presence of metabolic syndrome (MS) among categories of glucose regulation.

subjects (Appendix). The presence of MS was not associated with differences in age, HbA1c and total cholesterol within each glucose tolerance category.

IR (HOMA-IR >75° percentile of NGT subjects) was more common among IGR individuals than NGT subjects (42% vs. 25%; X^2, $p < 0.0001$), increasing with the deterioration of glucose tolerance (ANOVA $p < 0.0001$). Individuals with IFG + IGT had a higher rate of IR than those with an isolated defect (IFG + IGT, 53%; IFG, 45%; and IGT, 38%; $p < 0.0001$). IR also was more prevalent among subjects with than in those without MS (63% vs. 23%, $p < 0.0001$). The prevalence of IR increased according to the MS traits number: 5%, 23%, 39%, 54%, 73% and 88% in the presence of 0, 1, 2, 3, 4 or 5 traits, respectively (p-trend <0.0001). In spite of the strong association between MS and its traits and IR, no more than 59% of subjects with IR had MS.

As expected, the behaviour of the insulinogenic index mirrored that of HOMA-IR, so that while the latter progressively increased with worse glucose tolerance, the former progressively declined, being lower in all IGR groups than in NGT (ANOVA $p < 0.0001$). Moreover, there was no difference in the insulinogenic index between subjects with and without MS within each glucose tolerance category, while HOMA-IR was higher in subjects with MS (ANOVA $p < 0.0001$) (Figs. 3 and 4).

Irrespective of IDF or IDF/AHA/NHLBI definition, subjects with MS had higher levels of HOMA-IR than those without in each glucose tolerance group (data not shown). On the contrary, no significant differences were observed in the level of insulinogenic index between subjects with and without MS.

Seventy percent of subjects with MS were identified by three traits, while 30% of subjects with MS had more than three components. Obesity, hypertriglyceridaemia, low HDL and hypertension accounted for the most frequent association (>50% of the cases). To further explore the relationship between MS traits and IR, we evaluated the predictive values for IR of different triplets. The highest predictive power to identify subjects with IR (PPV 50—100%) occurred with triplets including hyperglycaemia and/or obesity. In subjects with IGR, a multiple logistic analysis, adjusted for age and gender, showed that hypertriglyceridaemia (OR: 3.38; 95% CI: 2.29—4.99), abdominal obesity (OR: 3.26; 95% CI: 2.18—4.89), hyperglycaemia (OR: 3.02; 95% CI: 1.80—5.07) and hypertension (OR: 1.69; 95% CI: 1.12—2.55) were all independently associated with IR.

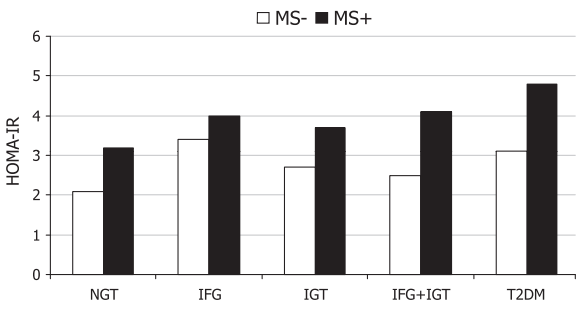

Figure 3 HOMA-IR levels according to the presence of metabolic syndrome (MS) among categories of glucose regulation. *p<0.0001, **p<0.001.

Discussion

The GENFIEV study was initiated in the attempt to identify phenotypic and genotypic features that may help in improving risk stratification for T2DM development. While final results with respect to this principal aim are still awaited, the study clearly shows that an opportunistic screening performed in individuals anticipated to be at risk of T2DM by their primary care physician and referred to a diabetes clinic for further assessment, can identify more than 15% of unknown T2DM and a large number of subjects with IGR (37%). These figures are greater than the ones reported using population-based screenings [23,24]. Although this is not an unexpected finding, it should be appreciated that the process also enhances the identification of individuals at increased risk of cardiovascular disease because of multiple concomitant metabolic alterations, that is, people with MS. Thus, in subjects with IGR, the prevalence of MS was twice as much as the one we have previously reported in the general Italian population (33% vs. 17%) [25] while confirming a greater prevalence in the female than in the male gender, as previously observed [25—27]. The prevalence of the MS in IGR subjects reported in the literature varies widely, most likely due to the different definitions used for the diagnosis of both glucose tolerance and the syndrome. Accordingly, we observed that the prevalence of MS based on NCEP—ATPIII definition was slightly lower in comparison to the prevalence found with

the IDF or IDF/AHA/NHLBI criteria (33% vs. 36.5% vs. 38.2%), a difference largely explained by the lower threshold for waist circumference proposed for Europids by the latter. In the Botnia study [9], MS was defined according to the World Health Organization (WHO) criteria and diagnosed in 10% of NGT, 50% of IFG/IGT and 80% of T2DM subjects. In the Telde study [24], the prevalence of MS was based on IDF consensus and its prevalence was 13.2% in NGT, 57.2% in isolated IFG (FPG < 100 mg dl^{-1}), 64.4% in isolated IGT, and 75.6% in IFG + IGT group. In all cases, IGR appears to be associated with high rates of MS, irrespective of ethnic and geographical influences.

FPG is currently used in the definition of the MS, but recent studies have suggested that the assessment of glucose tolerance by an OGTT may improve the diagnostic performance [28,29]. In our study too, when the 2-h glucose was considered, the prevalence of MS exceeded 50%.

HOMA-IR level increased progressively with the deterioration of glucose tolerance, and the presence of MS was associated with the impairment of insulin sensitivity, independently of the definition used to classify the MS. In our population, an effect of MS was present in NGT subjects as well.

IR is commonly associated with compensatory hyperinsulinaemia. In line with this paradigm, both plasma insulin and C-peptide concentrations were higher in all IGR groups with MS in comparison with those without. In spite of that, there was no apparent difference in the insulinogenic index, suggesting that even within individuals at risk of T2DM IR, rather than impaired insulin secretion, is more strongly associated with MS. This finding has been much less explored in people with MS and in relationship with their degree of glucose tolerance. The available information is largely limited to the Asian population. Thus, Rhee et al. [16] in 322 Korean subjects at risk of T2DM showed that individuals with IFG and/or IGT or newly diagnosed diabetes with MS were more insulin resistant and presented a worse beta-cell function in comparison with those without MS. Similar data were reported by Mori et al. [30] in IGT Japanese subjects.

In summary, IR is a characteristic finding in subjects with IGR [13]; it predicts development of T2DM [31,32] and is a common defect underlying MS [33]. However, some difference seems to emerge among categories of glucose tolerance with the IFG + IGT group being characterised by the highest rate of IR. Several authors [34–36] have reported an increase of IR in IFG, IGT and IFG/IGT groups. By contrast, Heldgaard et al. [37] found no differences in IR between IFG and IGT. On the other side, in the Botnia study [26] as well as in the RIAD study [38], IR was mainly apparent in IFG than in IGT subjects. In the Telde study [24], all IGR categories were more insulin resistant as compared to NGT individuals. The reasons for these discrepancies are not readily apparent but difference in the population recruited in the different studies may well account for it.

IR has been proposed both as an independent cardiovascular risk factor [39,40] as well as a key player in pathophysiology of the MS [41]. The latter has been based on the recurrent association between IR estimates, the syndrome and its individual components [42]. Thus, in non-diabetic subjects, the prevalence of MS and the number of the components have been shown to increase as a function of IR [43]. In the Bruneck study [23], in subjects with multiple metabolic disorders, the prevalence of IR was 95.2%, to drop to 42% in overweight subjects with no metabolic disorders. A similar result has been reported by the European group for the Study of Insulin Resistance (EGIR): about 20% of overweight but otherwise healthy subjects had IR values (euglycaemic hyperinsulinaemic clamp technique) in the top deciles of insulin sensitivity distribution of normal-weight, healthy subjects [44]. By using NCEP-ATPIII criteria, a more recent study found that approximately two-thirds of the individuals with MS were also insulin resistant [45]. In agreement with the previous studies, we too report a relationship between IR and both the prevalence and the severity of the MS (i.e., the number of traits) in subjects with IGR. In spite of repeatedly reported association between IR and MS and the potential mechanism(s) linking IR and the alterations encompassed in the MS, it is somewhat surprising that, in our analysis, only half the subjects with IR didn't meet the criteria for the MS and, conversely, a large proportion of individuals with MS were not insulin resistant. We should approach with some caution the absolute values of our figures since IR was arbitrarily defined for HOMA-IR values above the 75th centile of the HOMA-IR distribution in NGT subjects. It should be also emphasised that neither universal definition nor clear cut-off value for IR exists. The implication of these observations is that other mechanisms are likely to account for the clustering of components of the MS. For instance, visceral obesity [46], inflammation [47] and endothelial dysfunction have been proposed to underlie the syndrome. Alternatively, one should consider that IR and the MS may be two distinct clinical entities with a certain degree of overlap in their distribution. Recent studies have been indeed able to show that IR, MS and T2DM are all independent predictors of coronary heart disease [48]. It was Reaven who proposed that classical cardiovascular risk factors can be associated with IR in his most famous Banting lecture [13], but he was also the one to emphasise, in more recent times [49], that a substantial number of subjects not meeting the NCEP-ATPIII criteria may be insulin resistant and retain CV risk as well as that the NCEP-ATPIII criteria should not necessarily identify insulin-resistant individuals.

The concept of the MS has been the object of a recent appraisal [50]. Many uncertainties with regard to the MS were raised. One issue dealt with the definition of the syndrome and whether different combinations of the diagnostic criteria may be associated to equivalents CV risk. Three studies have assessed the relationship between ATP-III criteria for MS and measures of IR in non-diabetic subjects [45,51,52]. All of them reported that NCEP-ATPIII criteria had low sensitivity to identify IR measured by the hyperinsulinaemic–euglycaemic clamp, modified insulin suppression test (steady-state plasma glucose concentration) or minimal model. In the study by Cheal et al. [45], obesity (based on BMI) and lipids turned out to be the best measures to identify IR. Recently, Sierra-Johnson and colleagues [52] showed that waist circumference was the most accurate diagnostic criterion for IR. In our population, hyperglycaemia, hypetriglyceridaemia, obesity and hypertension were all independent predictors of IR. Moreover,

the presence of hyperglycaemia and/or obesity in the diagnostic triplet conferred the highest predictive power to identify IR among subjects with IGR. The power of these two parameters may be well explained by the fact that high FPG tends to occur in a greater proportion among subjects at risk for T2DM and that obesity was highly prevalent in our population.

In conclusion, the results of our study indicate that the prevalence of MS is increased in IGR individuals and in particular in those with IFG + IGT. In these subjects, the prevalence of MS was already as high as in subjects with overt T2DM, highlighting an early increase of cardiovascular risk and emphasising the need of early preventative measures. IR worsens with the worsening of glucose tolerance and is even more severe is the presence of the MS. However, IR is not a prerequisite for the development of the syndrome suggesting other factors may underlie or contribute to the clustering of cardiovascular risk factors in these individuals.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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Appendix
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.numecd.2010.03.006.

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