Moderate Alcohol Consumption, Dietary Fat Composition, and Abdominal Obesity in Women: Evidence for Gene-Environment Interaction

JERRY R. GREENFIELD, KATHERINE SAMARAS, ARTHUR B. JENKINS, PAUL J. KELLY, TIM D. SPECTOR, AND LESLEY V. CAMPBELL

Department of Endocrinology (J.R.G., K.S., L.V.C.) and Diabetes Centre (L.V.C.), St. Vincent’s Hospital, 2010 Sydney, Australia; Department of Biomedical Science (A.B.J.), University of Wollongong, 2522 Wollongong, Australia; Sequenom Inc. (P.J.K.), San Diego, California 92121; and The Twin Research and Genetic Epidemiology Unit (T.D.S.), St. Thomas’ Hospital, London SE1 7EM, United Kingdom

We examined relationships among alcohol intake, dietary fat composition, and total body fat (TBF) and central abdominal fat (CAF), independent of genetic confounders, and evaluated the modulating effect of genetic susceptibility. We studied 334 female twins (57.7 ± 6.7 yr) after excluding dietary underreporters. Diet was assessed by Food-Frequency Questionnaire and body fat by dual-energy x-ray absorptiometry. Moderate alcohol consumers (12–17.9 g/d) had less TBF (20.6 ± 5.6 vs. 24.8 ± 8.4 kg, P = 0.05) and CAF (1.2 ± 0.6 vs. 1.6 ± 0.7 kg, P = 0.03) than abstainers. In multiple regression, alcohol consumption remained independently associated with body fat distribution. In cotwin case-control (monozygotic twin) analysis, moderate alcohol consumption accounted for 300 g less CAF, independent of genetic and other environmental factors.

Gene-environment interaction analysis indicated that this association was limited to subjects at high genetic risk of abdominal obesity. There was no relationship between dietary fat composition and adiposity. However, in women at low genetic risk of abdominal obesity, subjects with polyunsaturated fat intakes in the highest tertile had about 50% less CAF than subjects with intakes in the lowest tertile (0.9 ± 0.4 vs. 1.6 ± 0.4 kg, P = 0.0007), an association absent in subjects with high genetic risk. In conclusion, genetic risk modulates relationships between dietary factors and adiposity. Lower abdominal fat may mediate associations between dietary intake and type 2 diabetes risk. (*J Clin Endocrinol Metab* 88: 5381–5386, 2003)

THE INCREASING GLOBAL prevalence of obesity has important health and economic consequences (1). Abdominal obesity, independent of generalized adiposity, predicts dyslipidemia, insulin resistance, type 2 diabetes, and cardiovascular disease (2). Genetic factors explain up to 60% of the population variance in total and abdominal obesity in females (3, 4) and may modify the effect of environmental influences on body fat distribution. In contrast to physical activity and hormone replacement therapy (HRT), which we have previously shown to predict lower abdominal fat in women (5, 6), the influence of alcohol and dietary fat composition is controversial.

The U- or J-shaped relationship between alcohol and mortality is a product of reduced cardiovascular (particularly coronary) mortality in light to moderate drinkers and excess, predominantly noncardiovascular, mortality in heavy drinkers (7–9). Approximately half of this cardioprotection is attributed to increased levels of fasting high-density lipoprotein cholesterol (9); reduced hemostatic activity (10, 11) and insulin resistance (12) may also contribute. Adjustment for fat distribution attenuates the relationship between moderate alcohol consumption and improved insulin sensitivity (12), suggesting that protective associations between alcohol consumption and type 2 diabetes (13, 14), and even heart disease risk, may be mediated by less abdominal fat. Reported associations between alcohol consumption and abdominal obesity are inconsistent (15–27), related, at least partly, to reliance on anthropometric surrogates (in place of direct measures of body fat) and confounding by genetic and other environmental factors.

The relationship between dietary fat composition and body fat distribution also remains controversial. Unlike animal studies, which suggest a possible protective role for polyunsaturated fat (28, 29), the association between dietary fat composition and human abdominal obesity, which has predominantly been assessed anthropometrically, is inconsistent (15, 27, 30–34). Interactions between dietary fat subtypes and genetic risk of abdominal obesity, which may explain some of this inconsistency, remain unexplored.

The twin study design is a unique experimental tool that allows quantification of the impact of environmental factors on specific phenotypes, independent of genetic and other environmental influences. Importantly, it also allows the detection of interactions between environmental factors and genetic risk (gene-environment interactions). The aims of this study of female twins were to examine 1) the association between light to moderate alcohol consumption and total and abdominal adiposity, independent of genetic and related environmental confounders; 2) whether these relationships are modulated by genetic susceptibility to obesity; and 3)
relationships between dietary fat composition and body fat distribution in relation to genetic risk.

Subjects and Methods

Study cohort

Four hundred thirty-seven nondiabetic female twins were recruited through a national media campaign via the St. Thomas’ United Kingdom Adult Twin Registry. All participants provided written informed consent. The study was approved by the Institutional Ethics Committees at St. Thomas’ Hospital (London, UK) (phenoype information collected) and at St. Vincent’s Hospital (Sydney, Australia) (data validation, analysis, and interpretation). Subjects were unaware of specific nutritional hypotheses. Twin pairs were phenotyped at a single visit. Zygosity was ascertained by questionnaire (35) and confirmed by multiplex DNA fingerprinting (PE Applied Biosystems, Foster City, CA) if uncertain.

Anthropometry and body composition

Weight (nearest 0.1 kg) and height (nearest 0.01 m) were measured and body mass index (BMI, kg/m²) was calculated. Waist (narrowest circumference between lowest aspect of ribs and anterior superior iliac crests) and hip circumference (widest circumference between anterior superior iliac crests and greater trochanters) were measured, and the waist-to-hip ratio was calculated. Body composition was measured by dual-energy x-ray absorptiometry (DXA) (Hologic QDR, Waltham, MA). Total body fat (TBF) was calculated as absolute mass (kilograms) and percentage (%CAF). Central abdominal fat (

TBF) was manually traced by a single investigator. Central abdominal fat (CAF) was expressed as absolute mass (kilograms) and as percentage of the total soft tissue content of this window (%CAF) (37). We have previously shown DXA-measured abdominal fat to be reproducible (36), was manually traced by a single investigator. Central abdominal fat (CAF) was expressed as absolute mass (kilograms) and as percentage of the total soft tissue content of this window (%CAF) (37). We have previously shown DXA-measured abdominal fat to be reproducible (coefficient of variation < 6%) and relate strongly to insulin sensitivity in women (36).

Dietary and alcohol assessment

Dietary and alcohol consumption were measured by the Oxford Food Frequency Questionnaire (38), derived from the semiquantitative food frequency questionnaire used in the Nurses’ Health Study (39). This validated survey (38, 40) estimated average intake over 12 months and was self-administered after instruction from a trained nurse as previously described in this cohort (40). Portion sizes were specified and frequency of consumption was recorded (38). Average daily macronutrient intake was expressed as percentage of energy intake (EI) (41). Standard alcohol portions and frequency of consumption were recorded and the average intake was calculated (grams per day and percentage of EI). Alcohol intake was divided into five categories: group I, abstainers (21%); group II, 0.1–5.9 g/d (48%); group III, 6–11.9 g/d (20%); group IV (moderate drinkers), 12–17.9 g/d (6%); and group V, 18 g/d or more (5%). Data were analyzed using the European Prospective Investigation in Cancer and Nutrition Group nutrient database (Institute of Public Health, University of Cambridge, UK) and the Composition Analyses for Food Frequency Estimates program. Dietary underreporters (n = 103), subjects in whom basal energy expenditure [calculated using body composition data (42)] exceeded reported EI, were excluded to remove potential statistical bias. We analyzed 334 female twins further: 180 monozygotic and 56 dizygotic twins and 98 singletons, whose cotwin underreported EI or had unrecorded data. Singletons were included in cross-sectional analyses only.

Lifestyle and socioeconomic status

Standardized questionnaires determined smoking and HRT use. Menopause was defined as amenorrhea of 12 months or more. Physical activity was assessed in a random subgroup (n = 200:102 monozygotic, 48 dizygotic, and 50 singletons) by standardized questionnaire (5). Socioeconomic status was based on current or most recent occupation (Registrar General’s Social Class; n = 200 who also reported physical activity). Higher socioeconomic status (n = 61) included professional, managerial, and technical occupations; lower socioeconomic status (n = 139) incorporated skilled, partly skilled, and unskilled occupations.

Statistical analysis

Results are mean ± sn, with the exception of cotwin case-control analysis (mean ± se). Multiple regression models were identified by a forward stepwise procedure (in 200 subjects with physical activity and socioeconomic status measures) with %TBF and %CAF as dependent variables; F-to-enter was set to 4. Candidate independent variables examined in these models included alcohol intake, age, physical activity, smoking, HRT, and socioeconomic status. ANOVA and χ² tests were used to compare continuous and categorical variables, respectively, across alcohol and socioeconomic categories. Because the phenotypic characteristics of same-pair twins may be influenced by common genetic and environmental factors, the use of standard statistical techniques may underestimate se and overestimate significance (43). Twin relatedness was therefore accounted for by the generalized estimating equation (GEE) (44). In analyses in which significance was not altered by GEE modeling, only adjusted P values are reported. P < 0.05 was considered significant. Data were evaluated using Statview 5 (SAS Institute Inc., Cary, NC) and Stata Statistical Software, release 5.0 (StataCorp, College Station, TX).

As previously described (5, 6, 40), the cotwin case-control model (monozygotic twin pair analysis) was used to estimate the association between environmental factors and total and abdominal adiposity, independent of genetic effects. Because monozygotic twins are genetically identical, within-pair differences in body fat must be due to the environmental factors for which the twin pairs are discordant. To exclude the influence of other environmental factors, this model was used to examine the influence of alcohol on body fat distribution in monozygotic twin pairs concordant for HRT use and smoking. Within-pair differences in TBF and CAF were compared by ANOVA.

The twin model was used to examine whether associations between alcohol and dietary fat intakes and adiposity are influenced by genetic risk of obesity (gene-environment interaction). As previously described (5, 40), associations between dietary factors and body fat and its distribution were compared in twins at high and low genetic risk of TBF and CAF. Briefly, 150 twins (116 monozygotic and 34 dizygotic), concordant for HRT use and smoking, were grouped separately into tertiles of TBF and CAF. Because body fat and its distribution are highly heritable (3, 4), we assigned a genetic risk category for TBF and CAF to a randomly selected twin from each pair, based on the respective TBF and CAF tertiles of her cotwin. The group of randomly selected twins were also divided into alcohol intake tertiles. Lowest (mean, 0.4 ± 0.4 g/d) and highest (mean, 15.6 ± 19.5 g/d) alcohol terciles and obesity genetic risk categories. The twin pairs included a factor ANOVA to test the variable interactions specific effects of genetic risk and alcohol intake on TBF. This was repeated for CAF. A gene-environment interaction was present if the interaction between alcohol consumption tertile and obesity genetic risk category was significant. Analyses were also performed for dietary fat intake. Mean intakes of each dietary fat tertile were: total fat, lowest tertile 26.7 ± 3.8%, highest tertile 38.4 ± 4.0%; saturated fatty acids (SFA), lowest tertile 9.6 ± 1.6%, highest tertile 16.0 ± 2.3%; monounsaturated fatty acids (MUFA), lowest tertile 8.9 ± 1.6%, highest tertile 13.9 ± 1.5%; and polyunsaturated fatty acids (PUFA), lowest tertile 4.1 ± 0.7%, highest tertile 7.9 ± 1.6%.

Results

The mean age was 57.7 ± 6.7 yr (range, 39–70 yr). Ninety percent were postmenopausal; 21% used HRT. Sixteen percent smoked and 29% were ex-smokers. Dietary composition is reported in Table 1. By BMI, 60% were in the healthy range (20–24.9 kg/m²), 28% overweight (25–29.9), 4% obese (≥30), and 8% underweight (<20). Subjects in the higher socioeconomic status group were younger (54.8 ± 6.2 yr vs. 58.5 ± 7.2 yr, P = 0.04), with slightly higher alcohol (6.4 ± 8.4 vs. 4.2 ± 5.7 g/d, P = 0.03) and energy (2350 ± 532 vs. 2141 ± 459 kcal/d, P = 0.01) intakes than those in the lower socioeconomic status group. Smoking, HRT, physical activity, and...
dietary composition were not different (data not shown). Despite similar %TBF, higher socioeconomic status was associated with lower waist (75.4 ± 7.0 vs. 78.7 ± 8.5 cm, \( P = 0.01 \)), waist-to-hip ratio (0.7 ± 0.1 vs. 0.8 ± 0.1, \( P = 0.02 \)), and %CAF (34.5 ± 10.9 vs. 38.0 ± 9.4\%, \( P = 0.045 \)). The latter was attenuated (\( P = 0.13 \)) after controlling for age, alcohol consumption, and EI.

**Alcohol consumption**

**Cross-sectional analyses.** Mean alcohol intake was 5.7 ± 9.6 g/d (range, 0–95.2; median, 2.4 g/d). Although age, HRT use, and physical activity were similarly distributed across alcohol consumption categories, more moderate alcohol consumers than abstainers were smokers (35 vs. 12\%, \( P = 0.01 \)). Moderate alcohol consumers had similar dietary composition to abstainers and light drinkers, apart from lower carbohydrate intake (\( P < 0.001 \)). Carbohydrate intake was, however, unrelated to %TBF and %CAF (not shown).

Table 2 shows anthropometry and body composition stratified by alcohol consumption category. Weight, BMI, and total adiposity decreased with increasing alcohol intake, particularly more than 12 g/d. Waist-to-hip ratio did not vary with alcohol intake (data not shown). The lowest measures of abdominal obesity were found in subjects with moderate alcohol intake (Table 2). Compared with abstainers, moderate alcohol consumers had 17\% and 25\% less total and abdominal fat, respectively. Exclusion of smokers (\( n = 51 \)) yielded similar results (data not shown). Differences between moderate drinkers and abstainers in %TBF (\( P = 0.01 \)) and %CAF (\( P = 0.03 \)) were maintained when physical activity and smoking were included as covariates in the 200 subjects with both measures.

In stepwise multiple regression models (\( n = 200 \) twins with physical activity and socioeconomic status measures), significant independent predictors of %TBF were physical activity (\( \beta: -0.20 \)) and alcohol intake (\( \beta: -0.15 \)), together explaining 6\% of the variance in %TBF. Thirteen percent of the variance in %CAF was explained by physical activity, alcohol intake, and socioeconomic status (\( \beta: -0.24, -0.21 \), and \(-0.15 \), respectively). After GEE modeling, although results were unchanged for %TBF, only physical activity and alcohol remained significant determinants of %CAF. The inclusion of fat and carbohydrate intakes as independent variables did not alter the results (data not shown).

**Cotwin case-control (monozygotic twin) analysis.** In monozygotic twins concordant for HRT use and smoking, pairs discordant and concordant for alcohol intake had similar within-pair differences in TBF (3.7 ± 1.3 vs. 2.7 ± 0.4 kg, \( P = 0.44 \)). However, discordance for moderate alcohol consumption was associated with significantly greater within-pair differences in CAF than concordance (0.6 ± 0.2 vs. 0.3 ± 0.0 kg, \( P = 0.01 \)). That is, independent of genetic HRT and smoking effects, moderate alcohol consumption accounted for a 300-g difference in CAF. In an analysis of monozygotic twin pairs discordant for alcohol intake (\( n = 6 \) pairs), twins with the higher alcohol intakes tended to have lower CAF than their cotwins (1.5 ± 0.7 vs. 1.9 ± 1.0 kg), although this was not significant due to the small number of discordant twin pairs (\( P = 0.45 \)).

**Gene-environment interaction analysis.** Although no gene-environment interaction was found for %TBF, there was a significant interaction between alcohol intake tertile and genetic risk category for %CAF (\( P < 0.05 \)). Whereas high genetic risk subjects with alcohol intakes in the highest tertile had less %CAF than the lowest tertile (37.0 ± 8.9 vs. 45.5 ± 6.8\%, \( P < 0.05 \)), in subjects with low genetic risk, %CAF was similar in the highest and lowest alcohol consumption tertiles (31.5 ± 10.9 vs. 27.8 ± 6.2\%, \( P = 0.39 \)) (Fig. 1). Within each genetic risk group, subjects with the highest and lowest alcohol intakes were similar in age, HRT, smoking, and, in the subgroup with this measure, physical activity. That is, in subjects genetically predisposed to abdominal obesity, a higher consumption of alcohol (within the moderate range) was associated with approximately 20\% less abdominal fat than lower intakes; no such relationship was found in low genetic risk subjects.

**Dietary fat subtype**

**Cross-sectional analyses.** Although there were relationships between total fat intake and weight (\( r = 0.14, P = 0.04 \)) and

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**TABLE 1.** Dietary composition in healthy female twins

<table>
<thead>
<tr>
<th>Dietary variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (g/d)</td>
<td>5.7 ± 9.6</td>
</tr>
<tr>
<td>Total energy (kcal/d)</td>
<td>2224 ± 593</td>
</tr>
<tr>
<td>Total fat %</td>
<td>33.9 ± 6.1</td>
</tr>
<tr>
<td>Saturated fat %</td>
<td>13.2 ± 3.8</td>
</tr>
<tr>
<td>Monounsaturated fat %</td>
<td>11.8 ± 2.5</td>
</tr>
<tr>
<td>Polyunsaturated fat %</td>
<td>6.0 ± 1.9</td>
</tr>
<tr>
<td>Carbohydrate %</td>
<td>48.8 ± 6.3</td>
</tr>
<tr>
<td>Protein %</td>
<td>16.8 ± 3.0</td>
</tr>
</tbody>
</table>

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**TABLE 2.** Anthropometric and body composition variables according to alcohol consumption category in healthy female twins

<table>
<thead>
<tr>
<th>Alcohol intake (g/d)</th>
<th>Categories of alcohol consumption (g/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All subjects ( n = 332 )</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.2 ± 9.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 ± 3.4</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>77.3 ± 8.1</td>
</tr>
<tr>
<td>TBF (kg)</td>
<td>24.2 ± 7.6</td>
</tr>
<tr>
<td>%TBF</td>
<td>37.9 ± 7.2</td>
</tr>
<tr>
<td>%CAF</td>
<td>36.5 ± 10.2</td>
</tr>
<tr>
<td>FFM</td>
<td>36.4 ± 4.2</td>
</tr>
</tbody>
</table>

Data are mean ± SD. FFM, Fat-free mass. All comparisons after GEE modeling

\( a \) \( P = 0.03; b \) \( P = 0.02; \) and \( c \) \( P = 0.04 \) compared to group I (abstainers).
had similar SFA, MUFA, and total energy and alcohol intakes. Age, HRT, and smoking prevalence and, in those in whom it was measured, physical activity, were also similar. Therefore, in subjects at low genetic risk of abdominal adiposity, an approximate doubling in PUFA intake was associated with halving of the abdominal fat mass, although there was no relationship in those at high genetic risk.

**Discussion**

Despite the strong genetic influence on body fat and its distribution in middle-aged women (3, 4), the identification of potentially modifiable environmental influences is important at both clinical and public health levels. In contrast to standard epidemiological studies, the twin study design provides a unique model by which the effect of specific environmental factors can be quantified, independent of genetic and related environmental confounders. In the current study, after controlling for age, physical activity, HRT, smoking, diet, and occupational social class, alcohol consumption was inversely related to directly measured TBF and CAF. Using cotwin case-control models in monozygotic twins to exclude genetic and other environmental effects, we found that a moderate alcohol intake was associated with 300 g less abdominal fat than abstinence or light drinking. Gene-environment interaction analysis showed that the association between moderate alcohol consumption and abdominal fat was dependent on genetic risk, with a protective effect evident in genetically predisposed subjects only. In these individuals, a daily intake of 1–1.5 alcoholic drinks was associated with approximately 20% less abdominal fat than individuals of a similar genetic risk with alcohol intakes equivalent to less than one drink per week. Despite the absence of an association between dietary fat composition and adiposity in the total cohort, subjects at low genetic risk of abdominal obesity with the highest PUFA intakes had almost 50% less abdominal fat than those with the lowest intakes.

The finding that moderate alcohol consumption was associated with lower directly measured abdominal obesity in healthy women, after controlling for important well-quantified confounders, is novel and clarifies conflicting results of previous studies, most of which have relied on anthropometric abdominal fat estimates (15–27). To our knowledge, only four other studies (45–48) have used direct body fat measures (DXA or computed tomography) to examine the alcohol-abdominal fat association, although none have included large numbers of predominantly normal-weight, postmenopausal, light to moderate alcohol consumers and simultaneously adjusted for important confounders, including physical activity and socioeconomic status. Two of these studies (45, 48) included significant numbers of heavier drinkers, possibly skewing the relationship.

This is the first report that genetic risk influences the association between moderate alcohol consumption and DXA-measured abdominal fat. Together with a recent study, which found that alcohol dehydrogenase type 3 genotype modifies the effect of alcohol consumption on myocardial infarction and high-density lipoprotein cholesterol levels (49), our study highlights the importance of genetic risk in...
determining relationships between alcohol consumption and metabolic syndrome phenotypes.

The reported relationship between dietary fat subtypes and abdominal obesity in women is controversial and inconsistent (15, 31, 33). This may be due to differences in study design, dietary assessment, cohort characteristics (including genetic risk), the use of anthropometric fat surrogates in place of direct measures of body composition, inclusion of energy underreporters, and unadjusted confounding factors. Our findings confirm previous cross-sectional studies using DXA (36, 40) and computed tomography, the latter reporting no relationship between dietary fat composition and visceral fat after adjusting for total adiposity (47, 50). Only two small studies have examined whether short-term changes in dietary fat composition influence body fat distribution in humans (51, 52). In the most recent, using magnetic resonance imaging, despite no change in visceral fat, sc abdominal fat was lower after a PUFA-rich diet, compared with a SFA-rich diet, in nondiabetic subjects, particularly in women (51).

The finding of a gene-environment interaction between PUFA intake and %CAF, with a beneficial association in subjects at low genetic risk of abdominal obesity only, is novel and may explain, in part, the conflicting findings of previous reports. We hypothesize that abdominal fat may be an intermediate between PUFA intake and reduced type 2 diabetes risk in women (53), particularly in those at low genetic risk of abdominal obesity. Putative genetic candidates, which may contribute to differential associations between PUFA intake and adipogenesis, have recently been reported (54).

The strengths of this study relate to the accuracy of body composition and dietary intake assessments and the exclusion of dietary underreporters. By studying twins, we were able to simultaneously control for genetic and environmental confounders and examine gene-environment interactions. Limitations, however, must be considered. Because the study was cross-sectional, causality cannot be determined. The results may not be generalizable to men or younger women. The exclusion of dietary underreporters may not have simultaneously excluded alcohol underreporters. The study did not evaluate the relationship between heavy alcohol intake, or specific alcoholic drinks, and adiposity. Finally, we did not distinguish between n-3 and n-6 PUFA.

In conclusion, this study reports novel gene-environment interactions between common environmental influences and genetic risk of abdominal fat in a large cohort of healthy, female, light to moderate alcohol consumers. Using direct measures of body composition and dietary intake, we found an inverse relationship between alcohol consumption and total and abdominal fat, independent of known environmental confounders. Compared with abstainers and light drinkers, women consuming 1–1.5 drinks/d had lower TBF and CAF. The gene-environment interaction suggests women with the greatest genetic risk of abdominal obesity may benefit more from this level of alcohol consumption than those at lowest risk. In contrast, a beneficial gene-environment interaction between PUFA intake and abdominal obesity was detected only in women at low genetic risk, with no association in subjects at high genetic risk of abdominal adiposity, suggesting that the effect of genetic predisposition overrides any environmental effect of PUFA consumption in this group. Our results raise the possibility that lower abdominal fat may partly explain reported associations between dietary factors and reduced risk of type 2 diabetes and cardiovascular disease.

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Address all correspondence and requests for reprints to: Professor Lesley Campbell, Director, Diabetes Centre, St. Vincent’s Hospital, 372 Victoria Street, Darlinghurst, 2010 Sydney, Australia. E-mail: l.campbell@garvan.org.au.

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