RESEARCH HIGHLIGHTS

Highlights from the latest papers in obesity research

Gül Bahtiyar, Girardin Jean-Louis, Fiby Nessim & Samy I McFarlane†

†Author for correspondence: Kings County Hospital Center, Division of Endocrinology, Diabetes and Hypertension, Department of Medicine, Box 50, State University of New York, Health Science Center at Brooklyn, 450 Clarkson Avenue, Brooklyn, NY 11203, USA; Tel.: +1 718 270 3711; Fax: +1 718 270 6358; e-mail: smcfarlane@downstate.edu

Rosiglitazone evaluated for cardiovascular outcomes – an interim analysis

Evaluation of: Home PD, Pocock SJ, Beck-Nielsen H *et al.*: Rosiglitazone evaluation for cardiovascular outcomes – an interim analysis. *N. Engl. J. Med.* 357(1), 28–38 (2007).

A recent meta-analysis by Nissen and Wolski [1] has raised serious concerns and generated considerable debate regarding the cardiovascular safety of rosiglitazone, a thiazolidinedione that is approved for treatment of hyperglycemia in people with diabetes. This meta-analysis suggested that rosiglitazone increased the risk of myocardial infarction by 43% and might also increase the risk of cardiovascular mortality.

Given the uncertainty and the considerable risk cited in Nissen's article, investigators from a large ongoing trial, the RECORD study [2], have decided to conduct an unplanned interim analysis. In this ongoing Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study, investigators present interim findings regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes.

The RECORD trial is a long-term, multicenter, randomized, open-label, head-to-head study that is being conducted in Europe. It is designed to determine whether the addition of rosiglitazone to either metformin or sulfonylurea (rosiglitazone group) is noninferior to the combination of metformin plus sulfonylurea (control group) in terms of cardiovascular outcomes that have been prospectively defined. There were a total of 4447 patients randomized with glycosylated hemoglobin values between 7 and 9% while taking maximum doses of either sulfonylurea or metformin. The degree of glycemia achieved in both arms was essentially identical. The primary outcome was either cardiovascular hospitalization or cardiovascular death. The follow-up time frame was planned to be 6 years. This interim analysis was conducted at 3.75 years, therefore significantly limiting the statistical power to detect meaningful differences between the two study populations.

A total of 217 patients in the rosiglitazone group and 202 patients in the control group had the adjudicated pri'nsmary end point (hazard ratio: 1.08; 95% confidence interval [CI]: 0.89–1.31). After the inclusion of end points pending adjudication, the hazard ratio was 1.11 (95% CI: 0.93–1.32). In addition, in this interim analysis there were no statistically significant differences between the rosiglitazone group and the control group regarding myocardial infarction and death from cardiovascular causes or any cause. However, there were more patients with heart failure in the rosiglitazone group than in the control group (hazard ratio: 2.15; 95% CI: 1.30–3.57), consistent with previous studies with thiazolidinedione.

With the inconclusive results from the RECORD study presented here, cardiovascular safety of the thiazolidinediones remains a major concern. However, awaiting the full analysis of the RECORD study and the publication of the cardiovascular outcomes of both the DREAM and the ACCORD studies, physicians should exercise caution when using these medications, particularly in high-risk populations.

References

1. Nissen SE, Wolski K: Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N. Engl. J. Med.* 356, 2457–2471 (2007).
2. Home PD, Pocock SJ, Beck-Nielsen H *et al.*: Rosiglitazone evaluated for cardiovascular outcomes – an interim analysis. *N. Engl. J. Med.* 357, 28–38 (2007).

Psychopathological predictors of compliance and outcome in weight-loss obesity treatment

Evaluation of: de Panfilis C, Cero S, Dall'Aglio E, Salvatore P, Torre M, Maggini C: Psychopathological predictors of compliance and outcome in weight-loss obesity treatment. *Acta Biomed.* 78(1), 22–28 (2007).

In 1981, an important review of the literature addressing behavioral treatment programs of obesity suggested several limitations of such programs. After evaluation of over 200 papers, authors of that review surmised that changes in weight were often small and predictors of such changes could not be adequately ascertained [1]. More recent behavioral weight-reduction studies have demonstrated short-term weight loss averaging 10% from baseline measurements [2]. One of the factors responsible for improvement in success rates has been the recognition that pre-existing psychological/psychiatric variables may influence treatment outcomes. Since obesity continues to rise, reaching epidemic proportions in the USA, it is paramount that behavioral treatment programs be effective in bringing about significant improvement in obesity-related illnesses and enhanced quality of life.

The study reported by de Panfilis *et al.* represents an important step in further identifying baseline characteristics predictive of positive outcomes of weight-reduction trials [3]. Previous studies evidenced that psychopathological measures are associated with outcomes in weight-loss programs, but it was not clearly discerned how those factors influenced subgroups of patients. In the article, de Panfilis *et al.* present results of their study investigating compliance and outcome in an 8-month behavioral weight-reduction program [3]. The main hypothesis of the study was that pretreatment psychopathological measures will allow the identification of obese patients at risk for poor compliance and/or poor treatment outcome. Investigators performed an extensive baseline assessment of several clinical and personality variables, including Axis I and Axis II disorders, depression and anxiety symptoms, eating attitudes and symptomotology, dimensional personality traits, temperament and character patterns, and alexithymia.

Regarding baseline risk factors for poor adherence and treatment outcome, the investigators found that the presence of an Axis I disorder promotes the likelihood of completing the 8-month treatment protocol, while lowering the probability of achieving desired weight reduction. This finding might have seemed paradoxical, since completion of the weight-management program would have suggested adherence to all recommended procedures and requirements of the program, thus achieving set goals. Plausibly, completion of the program by patients with psychiatric disorders might have been driven by a motivation to lessen the severity of their comorbid psychiatric conditions, seeking to alleviate further psychological distress imposed by weight problems. Unfortunately, such psychiatric conditions, while ensuring treatment compliance in obesity treatment programs, do not always translate into successful weight reduction. One possible explanation of this finding is that the type of alliance between the patient and the provider, which ordinarily promotes achievement of desired behavioral goals, is hindered by patients' psychiatric conditions. Other factors likely to influence treatment response among obese patients with psychiatric comorbidity include biological determinants and drug therapy, which were not explored in the present study. Nevertheless, the study advances our understanding of the importance of ascertaining baseline psychiatric disorders that could influence treatment outcome in weight-management programs. Replication of these findings in a large-scale study is necessary for a better delineation of the psychiatric determinants of treatment responses.

References

1. Foreyt JP, Goodrick GK, Gotto AM: Limitations of behavioral treatment of obesity: review and analysis. *J. Behav. Med.* 4(2), 159–174 (1981).
2. Wing RR: Behavioral weight control. In: *Handbook of Obesity Treatment*. Wadden TA, Stunkard AJ (Eds). Guilford Press, NY, USA, 301–316 (2002).
3. de Panfilis C, Cero S, Dall'Aglio E, Salvatore P, Torre M, Maggini C: Psychopathological predictors of compliance and outcome in weight-loss obesity treatment. *Acta Biomed.* 78(1), 22–28 (2007).

The spread of obesity in a large social network over 32 years

Evaluation of: Christakis NA, Fowler JH: The spread of obesity in a large social network over 32 years. *N. Engl. J. Med.* 357(4), 370–379 (2007).

Over the last two decades, obesity has become a worldwide epidemic, eclipsing malnutrition and infectious disease as the most important determinants of diseases [1]. According to the National Health and Nutrition Examination Survey, approximately two-thirds of US adults are overweight [2]. Commensurate with the rise in the prevalence of obesity is an increase in the rate of important medical illnesses (e.g., Type 2 diabetes and cardiovascular disease). The obesity epidemic has not been attributed to genetic underpinnings, as it affects individuals in all socioeconomic or ethnic groups [3]. Alarmed by such statistics, public-health

officials have pondered the causes of this dramatic rise in the prevalence of obesity, finding little evidence in support of behavioral health policies that could be implemented across socioeconomic groups to control obesity. The belief that obesity is fostered by individual choices (e.g., poor diet and a sedentary lifestyle) has been touted as one of the factors contributing to the failure to bring substantial reduction in those statistics.

Excitement greeted new findings from research conducted at Harvard Medical School (MA, USA) and the University of California at San Diego (CA, USA) indicating that obesity is not singly a matter of individual choices [4]. Using data collected between 1971 and 2003 from participants in the Framingham studies, investigators assessed the spread of obesity in the Framingham population and how it affected identified social and familial networks through established social network algorithm programs. Besides the hypothesis that social and family ties influence the spread of obesity, researchers also explored whether gender, smoking, socioeconomic status and geographic distance affected proposed associations.

The main finding of the study was that social distance, rather than geographical distance, contributed significantly to the spread of obesity. Specifically, the chance of individuals becoming obese increases by 57% if they had a friend who became obese. Furthermore, siblings of affected individuals have a 40% increased risk of obesity, and their spouses have a 37% increased risk. Interestingly, neighbors of individuals in that cohort have apparently no effect on observed risks if they do not belong to their social networks. Gender also played a meaningful role in the sense that individuals of the same sex had relatively greater influence on spreading obesity than did individuals of the opposite sex.

These data seem to offer solid evidence to support the development of public-health policies aiming at reducing the obesity epidemic through patient empowerment via existing social networks. If, indeed, social network is the mechanism through which obesity is spread, it can also be used to reverse the trends in this epidemic. Such policies might include greater investment in tailored weight-management programs with a strong emphasis on modifying maladaptive behavior patterns through interactions with peers. Behavior change processes occurring in a member of a particular network are likely to affect other members. It has been shown that programs focusing on changing participants' social networks are more successful than those that do not [5].

References

1. Kopelman PG: Obesity as a medical problem. *Nature* 404, 635–643 (2000).
2. Hedley AA, Ogden CL, Johnson CL *et al.*: Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *JAMA*, 291, 2847–2850 (2004).
3. Stunkard AJ, Harris JR, Pedersen NL, McClearn GE: The body-mass index of twins who have been reared apart. *N. Engl. J. Med.* 322(21), 1483–1487 (1990).
4. Christakis NA, Fowler JH: The spread of obesity in a large social network over 32 years. *N. Engl. J. Med.* 357(4), 370–379 (2007).
5. Wing RR, Jeffery RW: Benefits of recruiting participants with friends and increasing social support for weight loss and maintenance. *J. Consult. Clin. Psychol.* 67(1), 132–138 (1999).

Evaluation of BMI-based classification of adolescent overweight and obesity: choice of percentage body fat cutoffs exert a large influence. The COMPASS study.

Evaluation of: Neovius M, Rasmussen F: Evaluation of BMI-based classification of adolescent overweight and obesity: choice of percentage body fat cutoffs exert a large influence. The COMPASS study. *Eur. J. Clin. Nutr.* (2007) (Epub ahead of print).

Identifying children at risk for adolescent obesity provides physicians with an opportunity for earlier intervention, with the goal of limiting the progression of abnormal weight gain that results in the development of obesity-related morbidity.

Although the long-term effect of overweight and obesity on morbidity and mortality in children has not yet been well documented, several studies suggest that obesity in childhood is followed by serious consequences in adulthood [1]. The definition of childhood and adolescent obesity remains unclear and the cutoff points for overweight and obesity vary from above the 85th to above the 97th percentiles [2]. BMI (in kg/m^2) has achieved international acceptance as a standard for the assessment of obesity in adults and correlates with body fat (r = 0.7–0.8). In children, factors such as growth make definitions more complex [2]. Therefore, different methods have been used to estimate prevalence of childhood obesity. There have been several studies assessing the diagnostic accuracy of adipose tissue for classification of overweight and obesity based on body fat percentage (%BF) in adolescence [3,4]. It has been shown that the accuracy of most of the skinfold-thickness equations for assessment of %BF in adolescents was poor at the individual level [5] and over-represented the cardiovascular risk factors [6].

In this large population study, Nevious and Rasmussen pooled large numbers of data from the COMPASS study, a community-based study of physical activity, lifestyle and self-esteem in Swedish schoolchildren, and investigated the influence of three different %BF cutoffs on the diagnostic characteristics and usefulness of a commonly used BMI-based reference for detecting adolescent overweight and obesity [7]. They reported that for all three %BF cutoffs, the BMI-based classification was found to be highly specific, but insensitive, for both overweight and obese boys and girls. This means that the sensitivity and the total number of misclassified subjects varied greatly with the %BF cutoffs chosen, leading to much larger numbers of false negative results. Investigators concluded that the choice of %BF-reference in evaluations of BMI-based classification systems appears to have a large impact on the outcome and interpretation of evaluations of BMI as a screening measure. As the childhood obesity epidemic unfolds, additional studies are needed with definitive outcomes measures to better characterize obesity and establish reliable diagnostic criteria for the disease.

References

1. Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH: Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study from 1922 to 1935. *N. Engl. J. Med.* 327, 1350–1355 (1992).
2. Guillaume M: Defining obesity in childhood: current practice. *Am. J. Clin. Nutr.* 70(1), S126–S130 (1999).
3. Reilily JJ, Wilson J, Durnin JV: Determination of body composition from skinfold-thickness: a validation study. *Arch. Dis. Child.* 73, 305–310 (1995).
4. Neovius MG, Linne YM, Barkeling B *et al.*: Sensitivity and specificity of classification system for fatness in adolescent. *Int. J. Obes. Relat. Metab. Disord.* 29, 163–169 (2004).
5. Rodriguez G: Body fat measurement in adolescents: comparison of skinfold thickness equations with dual-energy X-ray absorptiometry. *Eur. J. Clin. Nutr.* 59(10), 1158–1166 (1999).
6. Williams DP, Going SB, Lohman TG *et al.*: Body fatness and risk for elevated blood pressure, total cholesterol, and serum lipoprotein ratios in children and adolescents. *Am. J. Public Health* 82(3), 358–363 (1992).
7. Neovius M, Rasmussen F: Evaluation of BMI-based classification of adolescent overweight and obesity: choice of percentage body fat cutoffs exert a large influence. The COMPASS study. *Eur. J. Clin. Nutr.* (2007) (Epub ahead of print).

Longitudinal changes in BMI and an index estimating excess lipid among white and black adults in the USA

Evaluation of: Kahn HS, Cheng YJ: Longitudinal changes in BMI and in an index estimating excess lipids among white and black adults in the United States. *Int. J. Obes. (Lond.)* (2007) (Epub ahead of print).

While BMI is traditionally used as measure of obesity in large population studies such as the National Health and Nutrition Examination Survey (NHANES) in the USA, change in BMI is limited by its predictive value of cardiovascular disease (CVD) risk. Furthermore, changes in BMI do not necessarily reflect changes in the amount or location of fat, particularly visceral fat. In this large population study [1], Kahn and Cheng pooled a large number of data from major studies that included a population sample comparable with that of NHANES, which is more or less representative of the US white and black population. Besides BMI, the authors used waist circumference (WC; in cm) and fasting triglyceride (TG; in mmol/1) concentration to describe lipid over-accumulation of the population (LAP), with a formula of LAP = (WC-65) × TG, for either men or women. The addition of LAP as a continuous index allows for estimation of accumulated lipids and perhaps provides a more realistic index of CVD risk than BMI.

In 1990, Williamson *et al.* looked into 10-year incidence of major weight gain in US adults using data from the NHANES I between 1982 and 1984, in which persons aged 25–74 years at baseline were reweighed a decade after their initial examination [2]. The incidence of major weight gain was twice as high in women and was highest in persons aged 25–34 years [3]. In this study by Kahn and Cheng, almost two decades later, the authors designed a nationwide, longitudinal, observational study of 16,763 white and black adults from three US cohorts that were developed to investigate cardiovascular risk (the study of Coronary Artery Risk Development in Young Adults [CARDIA], the Atherosclerosis Risk in Communities study [ARIC], and the Cardiovascular Health Study [CHS]) by assessing the annual BMI and LAP changes at two points in the period of time between 1989 and 1996. The three cohorts described in this study indicate close similarity to NHANES-III data.

For both sexes, the annual changes in BMI were greatest in young adults and almost reached zero at age 73–79 years. When compared with the data from NHANES-I, they found that the annual change in BMI is at least 0.1 U/year greater. The annual changes in LAP were predominantly positive across the cohort. The interquartile range of values for change in LAP among the younger man was approximately 3 cm mmol/l/year compared with 6–8 m mmol/l/year in men aged approximately 54 years and older. This information reveals that a substantial portion of the elderly population who are not gaining weight may continue to accumulate excess lipid with increased risk for CVD risk. It is likely that

these elderly persons who are accumulating fat without gaining weight have diminishing lean mass or lower-body subcutaneous adipose tissue.

Although the study introduces LAP as a viable substitute or complimentary measure of obesity, particularly in the elderly, the ability of LAP to predict disease outcomes remains to be established. Furthermore, the study is also limited by the absence of data on other racial groups, particularly Latinos and Asians, two of the fastest-growing minority populations with a relatively higher burden of obesity and CVD.

References

1. Kahn HS, Cheng YJ: Longitudinal changes in BMI and in an index estimating excess lipids among white and black adults in the United States. *Int. J. Obes. (Lond.)* (2007) (Epub ahead of print).
2. Williamson DF, Kahn HS, Remington PL, Anda RF: The 10-year incidence of overweight and major weight gain in US adults. *Arch. Intern. Med.* 150(3), 665–672 (1990).
3. Kahn HS: The "lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. *BMC Cardiovasc. Disord.* 6(1), 5 (2005).