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Editorial

Ethics in science

Rui Nunes

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Science, namely in biomedicine, has been able to reach all technological frontiers raising the question of what should be its ethical and social limits. It is true that the specific ethos of science is to contribute to make humanity better off allowing that people, all over the world, have access to the benefits of scientific evolution. Still there is no doubt that in many different settings, and at a global level, scientists have systematically disregarded basic ethical principles inherent to the human condition. Therefore, it is not surprising that in the last decades, namely after the Nuremberg trials, relevant conventions have been internationally proclaimed by different political institutions. But sharing the same ideals: to preserve the core values of humanity, especially human rights and human dignity, and obviously promoting the ideal that the interests of the subject should always prevail over the interests of science.

The Nuremberg Code, the World Medical Association Declaration of Helsinki, the Council of Europe’s Convention on Human Rights and Biomedicine, the UNESCO Universal Declaration on Bioethics and Human Rights or the Council for International Organizations of Medical Sciences International Ethical Guidelines for Health-Related Research Involving Humans are some examples of the need for international regulation of science and medical research. All of them, with no exception, suggest core ethical principles that should be universally respected. They can be summarised as follows: respect for persons and the need for free, informed consent; protection of incompetent persons, namely children and psychiatric patients (surrogate decision-making, proxy consent, living will, and so on); the ethical imperative to maximise benefits and minimise harms (beneficence and non-maleficence); privacy rights and confidentiality; justice/equity in the access to healthcare and to the benefits of clinical trials; accountability of healthcare professionals and institutions delivering healthcare; and responsibilities of ethical review committees.

Clearly, many moral dilemmas are related to cutting edge technology such as embryo manipulation, stem cell research, physical, cognitive and moral enhancement, cryogenic suspension of human beings, synthetic biology, genome editing and many other scientific programs that can temper with human dignity and even with human nature. On the other hand, ethical dilemmas may arise in clinical trials namely in multicentre research projects conducted by transnational pharmaceutical companies with the goal of developing innovative and revolutionary pharmaceuticals.

And how should humanity deal with these ethical challenges? What would be the ethical response of medicine to such dilemmas namely in a secular, pluralistic society? Indeed, different conceptions of the good are acceptable as long as the original position of the scientist is clearly stated and coherent with accepted foundational principles. Namely the ethical and legal principles endorsed by the international community.

Although the ethical regulation of science has many different forms, there is no doubt that professional autoregulation and especially personal integrity are paramount. It follows that there is a growing need to promote personal integrity as a core ethical value, both at medical training as well as throughout professional life, integrity should be valued, pursued and promoted. Both ethics committees (and institutional review boards) as well as professional organisations that regulate professional practice should be particularly aware of the importance of integrity in science and there should exist zero tolerance for deviated behaviours. It might imply a global strategy because science is propelled by huge transnational organisations, namely pharmaceutical companies. So, only truly independent regulatory bodies can defend the public interest and individual rights, namely the rights of the most vulnerable ones. Breaches of integrity can have many different faces, i.e. fabrication of data or reporting fake results, falsification research materials or changing or omitting data and even plagiarism, induced by financial gains, career progression, or institutional pressure.

Scientific journals should therefore promote more stringent guidelines in the evaluation, publication, and follow-up of the published research. As the genetic fingerprint of science is the search for the common good, the selection of referees for scientific papers is also a huge task for scientific journals because any proposed research should be evaluated in its ethical dimension and true authorships should be especially valued by the publishers. Again, zero tolerance should be the rule namely with plagiarism, manipulated data or results, or any other kind of scientific misconduct. And stringent mechanisms of accountability of the scientific community about these practices are needed, namely the public disclosure of scientists and research centres that engage in such practices.

But the ethical regulation of science should go even further. For instance the peer-review process should not only be fair and responsive but should also assure absolute confidentiality of the
research submitted for review. Therefore, any conflicts of interest both of the researchers as well as the reviewers are of utmost importance. Conflicts of interest of any nature namely the undue influence of transnational corporations who seek to make (legitimate) profit after huge investments in research. Indeed according to Forbes the average drug developed by a major pharmaceutical company costs at least $4 billion and it can be as much as $11 billion. Although it should not be questioned the corporate social responsibility of pharmaceutical companies, because they fill an important global gap in research, it is expectable (although not desirable) that sometimes maximising profit might be a compelling reason for some scientists to overcome their ethical duties.

Ethics in science is always an unfinished task. Only a joint effort of medical schools, professional associations, international regulatory bodies, and especially the personal integrity of researchers can reassure society that the ethos of science will always be the respect for the commonwealth of life.
Editorial

Cardiovascular precision medicine: Bad news from the front?

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A R T I C L E   I N F O

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Medical sciences have always been guided by evolving algorithms tailored to identify and stratify disease as well as to account for individual patient circumstances and adjust management accordingly. All interventions and surgical procedures are individualized. Medical practice has always been personalized and will remain so despite guidelines, carefully controlled clinical trials, evidence-based and protocol-based routines that often suggest a seemingly uniform treatment for specific conditions. Another prominent feature of medical science and practice is pragmatism. All theoretical research considerations and drug and technology developments are judged by their ultimate effects on patient and population health. Cardiovascular disease remains the main cause of death impaired quality of life and healthcare resource consumption in the Western world. In the last 50 years the most important development in medicine in the industrialized world was the decline of cardiovascular disease prevalence and lethality followed by a drop in mortality of some forms of cancer. Underlying this was a holistic prevention, pharmacology and intervention strategy. During the same period, major developments in biology have brought molecular research and genomics to the limelight of biomedical research. Advances stemming from the human genome project and the molecular biology field enabled affordable high-throughput complete gene analysis at many clinical research centres paving the way for integration of genetic data in medical sciences and patient management even for common prevalent conditions such as cardiovascular disease. This has led to the emergence of a new field dubbed precision medicine, first defined by Francis Collins as “using information about a person’s genetic makeup to tailor strategies for the detection, treatment, or prevention of disease”. Research in this field has been highly fostered and sponsored worldwide. Underlying this new revolutionary field are various strong premises: (i) that genes and information conveyed by DNA are the sole or main heritable components in living organisms, (ii) that genetic diversity is a consequence of random divergence and natural selection from a small founder population and therefore that a limited number of varying alleles that occur at a high frequency may explain the predisposition to disease (the common-disease common-variant hypothesis), and (iii) that DNA transcription in a few genome regions orchestrates protein synthesis and thus phenotype (Crick’s central Dogma of molecular biology). High expectations have been created for precision medicine, in Collins’ own words “it is hard to imagine that genomic science will not soon reveal the mysteries of hereditary factors in heart disease, cancer, diabetes, mental illness, and a host of other conditions”. On the other hand while clinicians were desperately seeking for answers in genes the central dogma of molecular biology and Neo-Darwinists’ Modern Synthesis have been progressively deconstructed by molecular biologists themselves. Indeed, extensive research in recent years has shaken the foundations of evolutionary biology and genetics and brought them back to the realm of physiology. Nobel Prize-winner Barbara McClintock placed the genome in an unusual spot as “an organ of the cell”, we now know that transposons are pervasive in the human genome and may have played a crucial role in evolution but many more other examples clearly document that genetic changes are almost always the result of cellular actions on the genome and that the cell should be better viewed as an active agent that reads and writes its genome over time according to clues from the environment in complex adaptive physiological processes, actually warranting a reappraisal of Lamarck’s work. Recent works also clearly documented heritability of non-genetic elements, not only of organelles such as mitochondria but also of the entire cell content. Cross-species hybrids derived from transferring the nucleus of an oocyte from one species to an enucleated oocyte from another species reveal that there is either arrest in development or a development course that is closer to the enucleated oocyte

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species thus phenotype is influenced both by DNA and cytoplasmic content. Indeed, transgenerational transmission of both non-genomic maternal and paternal as well as environmental influences through epigenetic mechanisms is highly likely and may have an important role in human health. Finally, it is now also realized that most of the DNA is not junk, that the processes that orchestrate gene transcription, protein coding and post-translational protein modifications are regulated by highly complex intertwined physiological processes and therefore that the outcome phenotype will also be very hard to predict. Indeed, this also partly explains variable penetrance and why large numbers of potentially pathogenic gene variants can be found in anyone of us. All of the aforementioned partly explain why genome-wide association studies have been able to identify genes and polymorphisms associated with the risk of common cardiovascular diseases, but usually showing minor or negligible relative risk and no ability to improve current traditional risk scores. Geneticists believe that it will be possible to predict genetic risk by increasing sample size of individual studies, combining studies, looking at population isolates and/or focusing on many more genes. Other experts advocate that only integration of multilevel omics (genomics, transcriptomics, proteomics, and other) with extensive clinical, epidemiological and functional phenotype at evolving time points will enable a systems biology view of cardiovascular disease relying on advanced statistical methodologies and big data analysis. The definition of precision medicine has therefore evolved to “treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations” with the ultimate aim of “improving clinical outcomes for individual patients and minimizing unnecessary side effects.” This daunting nascent task will warrant large collaborative international platforms to overcome regulatory, ethical, social and economic constraints in order to engage healthy and diseased individuals, practicing healthcare professionals and researchers as contributors to huge knowledge databases where overarching big data from multiple interoperable platforms including electronic health records and omics is uniformly integrated and made available for analysis by experts. Hopefully bioinformatics will extract valuable and relevant clinical information from these fuzzy logic systems by big data analytics. It is not clear how missing data, unmeasured confounding factors, treatment selection and sample selection biases or other known limitations for observational data will be accounted for by big data analytics. This and other concerns about big data analytics application to health care have been extensively reviewed. A recent report showed minor additive value of big data analytics to predict heart failure related hospital readmissions compared with simpler models. According to the most optimistic views we are living one of the most profound periods of progress in biology and medicine, experiencing a revolution whereby a global project of data collection, sharing and analysis will lead to evidence-based highly-effective precision medicine therapy and prevention, improved clinician-to-patient communication, improved citizen-centred healthcare and well-being. However experience often tells us that optimistic views, wishful thinking and moonshots are not the most profitable and pragmatic. Just as Candide eventually realized after a harsh course through life following his optimistic Leibnizian master Pangloss’s advice that he was better off cultivating his own garden (Voltaire, 1759), so we may come to the conclusion that eventually nothing will replace clinical, epidemiological and physiological research in medical sciences.

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Review article

Paediatric obesity and cardiovascular risk factors – A life course approach

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Abstract

Childhood obesity is increasingly prevalent worldwide, and Portugal presents one of the highest prevalence of obesity and overweight among the European countries. Since childhood obesity is a risk factor for obesity in adulthood, the high prevalence of overweight and obesity in paediatric age currently experienced is expected to lead to even higher prevalence of obesity in adulthood in future decades. It is well known that the prenatal period and infancy are critical or sensitive periods for obesity development, but a growing body of evidence also suggests a relevant role of childhood and adolescence. The exposure to some factors during these periods or specific time frames within these periods may confer additional risk for obesity development.

Paediatric obesity is associated with cardiovascular risk factors both in the short or medium-term, but also in the long term, conferring additional risk for future adult health. However, it is not clear whether the relation between paediatric obesity and adult health is independent of adult adiposity. There is a moderate to high tracking of obesity from paediatric age into adulthood, which may partially explain the association with adult outcomes. Therefore, there has been increasing interest on life course frameworks to study the effect of the dynamics of adiposity across paediatric age on adult outcomes, namely on the cardiovascular disease risk. The use of this approach to study determinants and consequences of obesity raises methodological challenges to summarize the exposure to adiposity/obesity across the life span, being the identification of growth trajectories and the quantification of the duration of obesity among the most used methods. However, further investigation is still needed to explore the best methods to summarize exposure to adiposity and its variation across time.

Paediatric obesity

Prevalence and trends

High prevalence of obesity is a major public health concern and obesity is acknowledged as a global pandemic. The Global Burden of Disease (GBD) Study 2013 reported an increase in worldwide prevalence of overweight and obesity between 1980 and 2013. The GBD Study 2013 used data from surveys, reports, and published studies with physical measurements or self-reported height and weight, and presents detailed estimates of overweight and obesity by region and country, for both children and adults. Data from this report estimated 2.1 billion overweight and obese individuals worldwide in 2013, reflecting the rise of 27.5% in the prevalence of overweight and obesity in adults and of 47.1% in children in the period from 1980 and 2013. The rate of increase was higher from 1992 to 2002, and slowed down in the past decade, particularly in developed countries, but prevalence is still increasing in most countries.

Considering the age strata, the analysis of trends in obesity prevalence over successive birth cohorts showed that the most rapid weight gains have occurred in the age group of 20–40 years, in both developed and developing countries, and that peak prevalence of obesity was moving to younger ages in developed countries. Prevalence of obesity in paediatric age has markedly increased since 1980, in particular in developed countries: from 1980 to 2013 it increased from 16.9% to 23.8% in boys, and from 16.2% to 22.6% in girls. In Portugal, information on national data on paediatric obesity collected by routine is scarce and surveillance initiatives on childhood obesity have been implemented just in recent years.

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data sources reported for Portugal 28.7% of overweight and obesity in children and adolescents (<20 years) for boys and 27.1% for girls, which is above the average estimate for the Western Europe: 24.2% and 22.0%, respectively. The WHO European Childhood Obesity Surveillance Initiative (COSI) was established in 16 countries to measure trends in overweight and obesity in children aged 6.0–9.0 years. Data collected in this context showed that Portugal was one of the European countries presenting the highest prevalence of obesity and overweight. In 2007/2008 prevalence of overweight (> 1 z-score, according to WHO growth reference) was 40.5% in 7-year-old boys and 35.5% in girls: the respective estimates in 2009/2010 were 31.5% and 36.2%. A previous cross-sectional national study developed in 2002/2003 had reported 20.3% of overweight (excluding obesity) and 11.3% of obese children aged 7–9.5 years, but using the IOTF criteria.

For Portuguese adolescents, repeated national data on obesity is available from the Health Behaviour in School-aged Children (HBSC), a WHO cross-national survey conducted every four years in 44 countries and regions across Europe and North America. The self-reported data showed that among Portuguese adolescents from the 6th, 8th and 10th grades there was 18.2% of overweight and obesity combined in 2014, according to the IOTF reference, and prevalence was higher in boys. The comparison with previous HBSC surveys showed stable estimates of overweight and obesity since 2002.

Objectively measured data on weight and height of adolescents is not collected at the national level in Portugal, on a regular basis. Only cross-sectional studies are available at national level in adolescents, and some cross-sectional or cohort studies at regional or local level. A national cross-sectional school-based study in 2008 including over 22,000 children and adolescents aged 10–18 years of age, found 17.4% of overweight and 5.2% of obesity, according to IOTF cut-offs. A review on obesity in Portuguese children and adolescents published in 2011, which included studies since 2007 from specific regions or communities, reported estimates based on IOTF cut-offs ranging from 13.4% to 28.6% in males and from 8.8% to 25.6% in females for overweight for adolescents (10–19 years); estimates for obesity varied between 3.2% and 13.0% in males, and from 0.6% and 5.8% in females. Longitudinal data is scarce, but in the EPITeen cohort, which recruited 13-year-old adolescents enrolled at schools of Porto in 2003/2004, the prevalence of obesity at the baseline was 11.3% in boys and 9.2% in girls and the prevalence of overweight 16.9% and 16.0% respectively for boys and girls, according to the CDC reference. Data from the follow-up of participants showed a mean decrease in the body mass index (BMI) z-score between 13 and 17 years, resulting in a decrease in the prevalence of obesity to 7.8% in boys and 3.8% in girls.

Although the lack of harmonized, objectively measured data, and collected on a regular basis on obesity in paediatric age in Portugal, available data suggest that Portugal presents one of the highest prevalence of paediatric obesity and overweight among the European countries. Since childhood obesity is a risk factor for obesity in adulthood, the high prevalence of overweight and obesity in paediatric age currently experienced by our country, as well as in most countries, is expected to lead to an even higher prevalence of obesity in adulthood in future years and decades.

Critical and sensitive periods for obesity development

A growing body of evidence shows that there are critical or sensitive periods across the life course for obesity development. Critical periods refer to specific stages of the development during which exposure to specific environmental stimuli may confer permanent anatomical or functioning changes with consequences for long-term effects of specific outcomes. These are specific time frames, during which exposures may confer increased risk of disease, but outside those time frames exposure to those factors do not confer additional risk of disease. A sensitive period refers to time frames of also rapid development, during which a greater effect of exposure to some factor is stronger in comparison to exposure outside that period, but that effect may be modified or reversed.

Foetal life is an example of a critical period, since tissues and organs systems undergo profound development and exposure to specific factors may irreversibly “programme” physiological functioning, playing an important role in disease aetiology. Adolescence, on the other hand, may be considered a sensitive period since a range of different developmental stages occur at variable time periods, and a specific critical period may not exist. However, in the literature the prenatal period, infancy, childhood and also adolescence are all usually identified as critical periods for obesity development.

Prenatal period and infancy

Regarding the pre‐natal period and infancy, observations that maternal nutrition could impact on offspring obesity were firstly described in the Dutch Hunger Winter Study in the 1970s. This study showed that 19-year-old males who had been exposed to famine in the first two trimesters of gestation, due to severe food rationing imposed in the winter and spring 1944–1945 during the Second World War, had higher prevalence of obesity, in comparison to those exposed in the other trimesters. Later epidemiological studies by Barker et al. 23–25 on the association between rates of infant mortality and adult deaths (ecological analysis) and on the association between birthweight and adult mortality from ischaemic heart disease conducted to the developmental origins theory, also known as the “Barker’s hypothesis”. This theory suggests that undernutrition during gestation may lead to foetal programming that changes body's structure, function, and metabolism with implication in the aetiology of adult coronary heart disease. This theory was later expanded to the Developmental Origins of Health and Disease (DOHaD) incorporating the effect of broader environmental exposures (nutrition, environmental chemicals, drugs, infections, or stress), not only in pregnancy but also in preconception period and in infancy, due to developmental plasticity, on widespread consequences for later health including obesity. In line with this theory several studies have shown that factors such as maternal obesity, nutrition and stress, exposure to chemicals during pregnancy and rapid postnatal weight gain are associated with obesity. Mechanisms might include epigenetic processes, such as DNA methylation, that alter gene expression and increase susceptibility for later disease, but also shared social influences across generations. The inter-generational effects of disease susceptibility seems not to be restricted to one generation, since some studies have shown associations across at least three generations.

Childhood

Adiposity rebound occurring at mid-childhood is also acknowledged as a critical period for obesity development. Adiposity increases during the first year of life, and then a decline is observed until a minimum (nadir) reached at approximately 6 years of age; the increase in adiposity registered after that nadir was firstly described as adiposity rebound by Rolland-Cachera et al. The timing of the adiposity rebound was shown to predict later adiposity levels; the earlier the age of adiposity rebound, the greater the degree of adiposity in adolescence and in young adulthood. Several studies have replicated the findings on the association between early adiposity rebound and obesity later in life. As shown by Taylor et al., the difference in BMI at 18–21 years can be around 3 BMI units higher for those with early adiposity rebound (<5 years), compared to those with late rebound (>7 years).
However, the utility of adiposity rebound for the prediction of later adiposity is controversial, since the rebound is identified based on at least 3 serial BMI measurements, meaning that it can only be identified after its occurrence. Additionally, adiposity rebound is based on BMI changes, which may not represent real changes in body fat.44,46 Reverse causation may also be a possible explanation for the association between timing of adiposity rebound and later adiposity, since early adiposity rebound has been suggested as a marker of early high BMI46,77 and of accelerated maturation.32,36 Two studies showed that BMI value at age 7 presented the same predictive value for later adiposity identification, in comparison to age of adiposity rebound.36,77 Therefore, although age at rebound seems to be predictive of later adiposity, it is not clear whether it is independent of childhood BMI, and it is difficult to measure since it requires several BMI measurements.

Adolescence

Adolescence is the second period of life, after infancy, characterized by intense growth.38 Additionally, it is one of the most complex periods in human growth, since in addition to increases in size, marked changes in body composition are also registered, and morphological signs of maturation are visible.16,38 Therefore, adolescence may also be critical for the development of obesity, due to changes in the amount and distribution of body fat.5,16,39 On one hand, fat cell number is determined by the end of adolescence and reversal of fat cell number is not possible during adulthood.39,40 On the other hand, sex-differences in the prepubertal body composition are modest, but the effect of sex hormones acting during pubertal development, such as oestrogen in girls and testosterone in boys, leads to sexual dimorphism in body composition.41,42 Females gain higher amounts of fat mass, especially peripherally, but relatively low fat-free mass, while in males there is a substantial acquisition of fat-free mass during this period, but relatively stable fat mass.41,42 Females enter puberty earlier and experience a more rapid pubertal transition, and therefore stop to grow at earlier ages, whereas boys have a longer growth period and attain higher final height.42 The combination of these changes in the absolute amount of fat and fat-free mass results in increasing percentage of body fat in females and decreasing in males during adolescence, resulting in 25% and 13% of body fat on average in adulthood, respectively for females and males.38,41 Sex-differences in body fat distribution are evident in body shape. In females, there is increased peripheral fat accumulation during puberty, especially on the hips and thighs, leading to a gynaecoid shape; in its turn, males have an android body shape, with greater accumulation of central fat, and relatively stable peripheral fat.31,42

The pubertal timing has also been described as a determinant of obesity. In females, several studies have shown that the earlier the age at menarche, the higher the risk of later obesity.41,44 A recent review found that from 34 studies addressing the association between age at menarche and adult BMI, the majority (30 out of 34) reported an inverse association.45 The meta-analysis of the 10 cohort studies identified in the review showed that girls with early age at menarche (<12 years) had higher adult BMI by 0.34 kg/m2 (95% CI 0.33–0.34).45 In boys, studies using age at peak height velocity as an indicator of maturation also reported an inverse association between timing of maturation and later adiposity.44,46

Additionally, some studies have shown that pubertal timing is also predictor of body fat distribution, however, evidence is still scarce and inconsistent, probably because the effects of body fat distribution and of total adiposity are difficult to separate. Data from the Amsterdam Growth and Health Study showed that early age at menarche in girls was associated with a trunk-oriented fat distribution pattern, while in boys age at peak height velocity was not.47 This sex-difference could be attributed to differences in the indicator of pubertal timing, however, another study in males using also age at peak height velocity showed an inverse association with central fat mass; early pubertal onset was associated with higher central fat mass.46

Although pubertal timing has been recognized as an indicator of later adiposity, reverse causation cannot be ruled out, since some studies have also shown that higher BMI at early childhood was associated with earlier onset of puberty.48,49 Therefore, higher adiposity may induce earlier maturation, and pubertal timing may be a mediator between early and later adiposity.

In addition to physiological changes taking place during adolescence, behavioural changes related to dietary, physical and sedentary habits that occur during this period may also increase the risk of obesity.39 Adolescence is marked by psychosocial and cognitive changes with impact on increased autonomy and behavioural change. There is a transition on the focus of the adolescent from the family to the peers,50,51 and adolescents progressively feel to be capable of managing themselves on their own, making decisions and solving their own problems.52 These transformations may be accompanied by new behaviours acquisition, for instance the initiation of health-related behaviours such as smoking, alcohol consumption, drugs use or sexual behaviours,53 and also changes in food intake and physical activity patterns.45,53 During adolescence an increase in sedentary behaviour and a decrease in physical activity is generally observed,54 being the decline in physical activity more pronounced in adolescent girls.56,57 These changes in physical activity and sedentary patterns during adolescence may have implications for weight gain in youth.56 Regarding food intake, changes during adolescence are related to increased adolescents’ autonomy over what, when and where they eat,59,60 which may lead to more unhealthy food choices. Studies have shown a decrease in breakfast frequency, and an increase in snacking and fast-food consumption during the period of adolescence.55,61 Additionally, time trends in adolescents’ food consumption have also shown increased frequency of snacking, meals eaten away from home, and consumption of fast food and energy-dense sweetened beverages.62 Furthermore, exposure to media seems to also play an important role in adolescents’ habits related to the risk of obesity, by promoting more sedentary activities, consumption of unhealthier foods, and conveying unrealistic thinness as the ideal for beauty.63 Changes in food and physical activity and sedentary habits during adolescence have impact not only due to short-term consequences on weight gain, but also long-term effects because these behaviours formed during adolescence tend to track into adulthood.64–66

Tracking of paediatric obesity into adulthood

A growing body of evidence has shown that obesity in paediatric age tends to track into adulthood. Evidence from the Fels Longitudinal study, which prospectively followed 555 participants throughout paediatric age, showed that BMI in childhood and adolescence was predictive of overweight/obesity at age 35 years.67,68 Data from the Bogalusa Heart Study also found that BMI in childhood was associated with adult adiposity levels: overweight children were about four times more likely to become overweight adults.69 Different studies have also shown that the risk of adult obesity increased with childhood age at BMI measurement.67–70 Guo et al.68 showed that the probability of obesity at 35 years increased with increasing age of participants with BMI at or above the 95th percentile: probability of adult obesity was lower than 30% for children aged 5 years with BMI at or above the 95th percentile; between 30% and 60% for girls between 5 and 12 years, and for boys between 5 and 18 years, in that percentile; and above 60% for older adolescents. In the Bogalusa Heart Study, the prevalence of obesity in adulthood was 86% in men and 90% women among those who were obese at age 15–17 years, while estimates were 76% and 78%
for those who were obese at 9–11 years. Whitaker et al. showed that odds ratio for adult obesity was 1.3 (95% CI 0.6–3.0) for obese children at 1 or 2 years of age, but much stronger (OR = 17.5, 95% CI 7.7–39.5) for obese adolescents at 15–17 years of age.

The evidence provided by these and other more recent studies was summarized in three systematic reviews, which consistently show the tracking of obesity from childhood into adulthood. Serdula et al. in a review including studies from 1970 to 1992, found that although correlation between BMI in childhood and adulthood varied considerably, obese children were at least two times more likely to be obese in adulthood, in comparison to nonobese children. Their results also supported a stronger association with adult obesity when obesity was present in older children, compared to younger. A later review also found that the risk of overweight tracking was higher for youth presenting higher levels of adiposity, and at older ages—risk of adult overweight was stronger for those who were overweight or obese in adolescence than in childhood. Finally, a systematic review and meta-analysis published in 2016 and including fifteen prospective cohort studies showed that the risk of being obese in adulthood was about five times higher for obese children and adolescents, in comparison to children and adolescents who were not obese. Among obese adolescents, 80% were still obese in adulthood.

Paediatric obesity and cardiovascular risk factors

Obesity-related risk factors

Obesity is associated with increased risk of various disorders from different systems, such as cardiovascular, endocrine, pulmonary, gastrointestinal, and psychosocial, and also with cause-specific and all-cause mortality. Overweight and obesity were estimated to cause of 3.4 million deaths worldwide in 2010, and it has been suggested that the increasing trend in obesity may revert progresses in life expectancy.

The association between obesity and cause-specific mortality is stronger for cardiovascular disease and diabetes, in comparison to other diseases. The Prospective Studies Collaboration, analysing data from 57 prospective studies with almost 900,000 participants, showed that each 5 kg/m² higher BMI was on average associated with about 40% higher vascular mortality (HR = 1.41, 95% CI 1.37–1.45), and 120% higher diabetes mortality (HR = 2.16, 1.89–2.46), while estimates were 10% for neoplastic and 20% for respiratory mortality. Abdulrahman et al. also showed that the number of years lived with obesity was directly associated with the mortality risk, and was higher for cardiovascular disease-cause than for cancer-cause mortality.

Given the strong association between obesity and cardiovascular-related mortality, and the high prevalence of obesity, as well as the burden of cardiovascular diseases worldwide, the study of the association between obesity and cardiovascular diseases is of great relevance from a public health perspective. Additionally, as the increase in childhood obesity occurred mainly from 1980s onwards, the first generation with high prevalence of obesity since early ages have not reached the life decades of higher incidence of cardiovascular events (the fifth decade of life onwards) yet. Therefore, the magnitude of childhood obesity consequences, in general and specifically on cardiovascular diseases, are not fully understood yet, and there is particular interest on extending evidence on the effects of childhood obesity on early markers of cardiovascular disease.

Cardiovascular events, such as stroke and ischaemic heart disease, are more frequent from the fifth decade of life onwards. Therefore, limited evidence from longitudinal studies is available on the effect of childhood obesity on adult cardiovascular events, due to the difficult operationalization of studies with such long follow-up periods. The establishment of birth cohorts intending to follow children throughout the paediatric age and during adulthood will provide important insights into this field, but until now most evidence is available for cardiovascular risk factors, rather than cardiovascular events.

The term ‘risk factor’ was first described by William B. Kannel in 1961, in the context of the Framingham Heart Study. According to the Dictionary of Epidemiology, a risk factor is a characteristic that is known to be associated with increased probability of an outcome, such as a disease, being denominated as a risk marker if it is not necessarily a causal factor. In the Framingham Heart Study, Kannel and colleagues found that elevated serum cholesterol levels, hypertension and electrocardiogram abnormalities increased the risk of heart disease. Since then, research from the Framingham Heart Study and other studies have identified other risk factors, such as diabetes, smoking, physical inactivity, and obesity, and these factors are usually referred as classical or traditional risk factors of cardiovascular disease. Other factors more recently identified include inflammatory markers, abnormal blood coagulation, homocysteine, among many others, and are described as novel cardiovascular risk factors. An extensive list of independent cardiovascular risk factors have already been identified, but the predictive ability and clinical implications of the novel risk factors is not so well identified yet, and traditional risk factors seems to explain most part of the cardiovascular diseases incidence and mortality. A study from the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration quantified attributable deaths from risk factors worldwide in 2010, and showed that 63% of deaths due to cardiovascular diseases, chronic kidney disease, and diabetes were attributable to the combined effect of four metabolic risk factors: high blood pressure, BMI, glucose and cholesterol. In Portugal, estimates from GBD for 2013 showed that high systolic blood pressure, dietary factors, and high body-mass index were the leading risk factors of Disability-Adjusted Life Years (DALYs), mainly related to cardiovascular diseases and diabetes.

Childhood obesity has been found to be associated with increased risk of cardiovascular risk factors as early as in preschool aged children. Most studies have addressed the association for obesity at specific ages, consistently showing that higher adiposity at any age is associated with increased risk of cardiovascular risk factors or events. However, most studies have not taken into account the dynamics of adiposity/BMI across the paediatric age, and the effect of different adiposity trajectories during the life course on adult cardiovascular risk profile is not so well understood.

Studies have evaluated the effect of childhood obesity on adult cardiovascular risk factors, but the results are controversial regarding the effect of childhood obesity independently of adult obesity. One study found no evidence for an association between childhood obesity on adult cardiovascular outcomes, but in general other studies have reported direct associations, although suggesting that the effect was mediated by adult obesity. Two other studies found an association of childhood obesity, but they had not taken into account the potential mediated by adult obesity. A systematic review published in 2010 and including 16 studies on the effect of childhood obesity on adult cardiovascular disease risk found that the association observed for childhood obesity was dependent on the tracking of BMI into adulthood, and that there was little evidence for the independent effect of childhood obesity. A more recent systematic review including thirty-seven studies which analyzed the ability of childhood BMI to predict obesity-related morbidities in adulthood concluded that childhood BMI was not a good predictor of adult morbidity, because most obesity-related morbidity occurred in adults who were normal weight children. However, most of the studies included in this review were from older cohort studies with
relatively low prevalence of obesity in childhood, and therefore it is important to understand if those findings would be replicated in more recent cohorts with higher prevalence of childhood obesity.

The measurement of independent effects of childhood obesity on morbidity is challenging in terms of the statistical analysis, since childhood and adult obesity are strongly correlated. Several studies have addressed this question using standard regression models, adjusting the association for adult BMI or obesity. Nonetheless, this adjustment may introduce over-adjustment bias and collinearity problems. This adjustment may also interfere with the interpretation of the results, since the adjusted estimates represent the effect of change in adiposity between measurements, and not only the effect of childhood adiposity adjusted for adult adiposity. Therefore, more sophisticated statistical techniques, such as structural equation models, may be more appropriate to study the effect of childhood obesity on adult outcomes. For example, in models such as path analysis direct and indirect effects can be estimated and results are easily interpretable.

In the studies measuring the association between childhood obesity and adult cardiovascular outcomes, the need of long follow-up periods may determine some limitations, such as limited information on the exposure for the interim periods. The associations estimated for childhood obesity may be confounded by subsequent changes in obesity throughout the paediatric age that are not measured in some studies. Additionally, changes in the grade of adiposity, and the duration of obesity are also not taken into consideration in most of the studies. Therefore, there is growing interest in studying the effect of paediatric obesity on adult outcomes, taking into account the exposure across the life course of the individuals.

Most evidence about the consequences of childhood obesity is based on the study of BMI, and therefore on the effect of total adiposity. However, the methodological challenges discussed here also apply to the study of the effect of body fat distribution. Moreover, there are additional challenges when studying body fat distribution, since it is not clear what is the best indicator of body fat distribution, namely to measure its effect beyond the effect of total adiposity.

Life course approach to the association of obesity with CV risk factors

The recognition that chronic diseases have long latency periods and their origins early in life led to the need of addressing the impact of different exposures acting across different periods of the life span, and of taking into account the timing of the exposures. Therefore, there has been increasing interest on life course frameworks to conceptualize the aetiology of chronic diseases. The life course epidemiology is defined as the study of long term effects of biological, behavioural, and psychosocial factors acting at different stages of the life span on health or disease risk. It addresses the influence of factors that operate across the individual’s life course, and also across generations, recognizing the importance of time and timing for establishing causality between exposures and outcomes.

Different theoretical models in life course epidemiology have been proposed. The critical period model emphasizes the timing of the exposure – an exposure acting at a specific period may have long lasting and irreversible effects on anatomical structure or physiological functioning (‘biological programming’). However, as discussed earlier in this paper, there may also be sensitive periods, where the effect of an exposure is amplified when taking place at a specific period. These two concepts share the importance of the timing of exposures for the risk of later outcomes. Another main class of life course models is based on the accumulation of risk, which suggests that effects of exposures accumulate over time. In the accumulation risk models, the timing could also be a key issue, being possible to have developmental periods when exposures have greater impact. Depending on the exposures and outcomes, accumulation of risk may occur through independent, clustered exposures or chains of risk. In the context of non-communicable diseases, the most common model is the risk clustering, where different adverse exposures tend to cluster (for example, health-related behaviours, or adverse exposures related to adverse social circumstances). The chains of risk, where one adverse exposure may lead to another, are also common, and the accumulation of risk may happen in an additive way or with trigger effects, when the final link in the chain has a marked effect on the risk of disease. All of these models are a simplistic representation of the effect of life course exposures and may be difficult to distinguish. Furthermore, the development of chronic diseases likely results from the interplay of critical periods and accumulation risk models.

Given the natural history of cardiovascular diseases with long latency periods and the recognition that early life factors are linked to the development of the disease, the use of a life course approach may provide insight into the comprehension of disease aetiology. Additionally, obesity itself is also influenced by factors acting at different stages over the life course. Therefore, the application of a life course framework for the study of the associations between obesity and cardiovascular disease may be of great relevance for understanding the effects of early obesity and its dynamics across the life span on cardiovascular health. Additionally, this approach has contributed to the better understanding of the interaction of factors occurring throughout life and the association with cardiovascular diseases, and also to the development of new methodologies to study how exposure to obesity across paediatric age impacts on cardiovascular disease.

One strategy to summarize the exposure to obesity has been to specifically investigate the effect of obesity duration, usually assessed through the age of obesity onset. However, results are conflicting since while some studies found no association, others have shown that higher duration of obesity was associated with worst cardiovascular risk profile in adulthood. One of those studies has additionally found that the increased risk of impaired glucose metabolism for those with higher duration of obesity was partly explained by attained adult adiposity. Some inconsistent results between studies may be due to differences in the age of participants under evaluation and in the definition of the outcomes. Additionally, the error in the measurement of duration of obesity using the age of its onset may differ between studies, depending on the total length of follow-up and number of measurements across the period under study.

Another study has suggested the use of “obese-years” as a good indicator of obesity-related health risks. Abdullah et al. showed that the obese-years, which summarizes duration and grade of obesity, was associated with increased diabetes incidence, suggesting that obese-years was a better indicator of the health risks than BMI or duration of obesity alone. However, both approaches, the duration of obesity and the obese-years, only take into account time lived with obesity (BMI at or above 30 kg/m²), and do not consider fluctuations of adiposity within normal BMI ranges. These approaches assume that health risks are associated only to BMI values above a specific threshold, which is not supported by previous evidence. Therefore, in general the assessment of the dynamics of adiposity has been simplistic, and most studies do not evaluate duration and grade of adiposity. For that reason, new methodologies to assess the exposure to adiposity, including duration and degree of BMI within the whole BMI spectrum, are warranted.
Another interesting approach to address the lifetime risk associated with obesity is the identification of adiposity trajectories over the life course. The study of growth trajectories in paediatric age has been recognized of great relevance for surveillance and for clinical practice, but it is also very useful for aetiology research. Studies have applied different methodologies for growth modelling in paediatric age. Some studies have identified individual growth trajectories through the application of mixed-effects models, where random effects capture individual variation across time. Other studies have applied a group-based statistical method, where subpopulations characterized by distinct developmental trajectories are identified. Part of this has studied the effect of growth trajectories on cardiovascular risk factors or metabolic outcomes. Generally, studies have found that groups experiencing growth trajectories characterized by higher adiposity, and specially with early obesity onset, are associated with the most unfavourable cardiovascular outcomes. Ventura and colleagues showed that girls in the highest metabolic risk factors at 15 years, while the ‘delayed downward percentile crossing’ presented similar levels in comparison to the ‘50th percentile tracking’. In the Raine Study, those in increasing trajectories from birth to 14 years presented the highest insulin resistance levels at 14 years, while the outcome in those from declining trajectories was similar to those in the reference trajectory. Data from the Isle of Wight birth cohort also found higher systolic and diastolic blood pressure at 18 years in the delayed overweight trajectory in comparison to the ‘normal’ trajectory, but still smaller than the values found for the early persistent obesity trajectory. In the EPITeen cohort, from Porto, Portugal, the ‘Higher BMI growth’ trajectory from birth until 21 years, as well as the ‘High, increasing’ BMI trajectory identified in the same cohort, but specifically in the period between 13 and 21 years, were associated with the most unfavourable cardiovascular risk profile at 21 years. Data from the Birth to Twenty (Bt20) cohort showed that trajectories of early onset obesity or overweight from 5 to 18 years had higher blood pressure levels in late adolescence. On the other hand, trajectories with a declining trend presented in general levels of cardiovascular risk factors between the trajectories of stable high adiposity or increasing trends, and the normal or optimal growth trajectories. As trajectories with declining adiposity trends approach final adiposity levels of the normal trajectories, these results may suggest that excessive gains in adiposity during the paediatric ages are associated with adverse cardiovascular risk factors, partly because it is likely to result in high final BMI.

Conclusions

This review highlights the relevance of taking into account the exposure to adiposity throughout the life span to better understand the role of adiposity as determinant of morbidity and mortality. However, this life course approach raises methodological challenges that have not yet been fully addressed and solved. Although it is still unclear what the best approach is, the study of the effect of BMI at different ages with adjustment for final attained BMI is recognized to present limitations. On the other hand, methods that take into account variations in adiposity across time, and also across the entire BMI spectrum, may be considered as superior approaches. Nevertheless, further investigation is needed to explore the best methods to summarize the dynamics of adiposity across time.

Conflict of interest

The authors declare no conflict of interest.

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References


Original article

Antidiabetic therapy at admission and survival in diabetic patients with acute myocardial infarction

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A B S T R A C T

Introduction: Diabetes mellitus is frequently associated to cardiovascular disease. We aimed at studying the relations between anti-diabetic drugs in use at admission by diabetic patients with acute myocardial infarction and survival after a period of at least 36 and up to 52 months after admission.

Methods: Retrospective study based on electronic records. Data from a total number of 195 admissions corresponding to different patients were under analysis.

Results: Kaplan–Meier analysis, as well as Cox analysis, failed to show a difference in survival associated to the use of DPP-4 inhibitors (n = 35 patients). A non-significant trend toward increased survival was seen with metformin (n = 92 patients), and in the opposite direction with both insulin (n = 51 patients) and sulfonylureas (n = 51 patients).

Conclusions: The use of DPP-4 inhibitors at admission, in patients with Diabetes mellitus admitted for acute myocardial infarction, was not associated to a different survival after no less than 36 months and up to 52 months after admission.

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Introduction

Diabetes mellitus is a highly prevalent disease, and is frequently associated to cardiovascular disease. Haffner et al. showed that diabetic patients without previous myocardial infarction had a risk of death from coronary heart disease similar to nondiabetic patients with previous myocardial infarction.1 Using data from the Multiple Risk Factor Intervention Trial, Stamler et al. showed that the presence of Diabetes mellitus was associated to an increased risk of cardiovascular death.2

Anti-diabetic therapy, however, has failed to produce consistent results in decreasing cardiovascular risk in diabetic patients, and in some cases an increased risk was in fact seen, starting with the seminal University Group Diabetes Program study.3 A particular concern was raised by the Action to Control Cardiovascular Risk in Diabetes Study, published in 2008, which showed an increased mortality associated to intensive anti-diabetic therapy.4

A considerable curiosity exists concerning the cardiovascular effects of newer anti-diabetic drug classes, including dipeptidyl peptidase 4 (DPP-4) inhibitor drugs. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 study, saxagliptin use was not associated to an increased incidence of major adverse cardiovascular events; however, an excess rate of hospitalization for heart failure was seen.5 In the Trial Evaluating Cardiovascular Outcomes with Sitagliptin study, the use of this latter drug was not associated to a change in the incidence of cardiovascular disease,6 the same happening in the Examination of cardiovascular outcomes with alogliptin versus standard of care 7 study. In this latter case, the study was carried out in patients with a recent acute coronary syndrome.

In a previous report, we retrospectively studied data on the relation between peak plasma troponin levels and anti-diabetic drugs (insulin, metformin, sulfonylureas and DPP-4 inhibitors) in use, from the admissions with acute myocardial infarction that took place during 15 months in an acute coronary care unit.8 In the present investigation, and using the same cohort, we aimed at studying the relations between anti-diabetic drugs in use at admission and survival after a period of at least 36 and up to 52 months after admission. The same cohort was previously studied using similar methods but addressing a different research question (the relation between plasma alkaline phosphatase and survival).9

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2444-8664/© 2017 PBJ-Associação Porto Biomedical/Porto Biomedical Society. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Methods

The present study was retrospective, and part of the methods have been described in previous reports,\(^8,9\) and are hereby reproduced. From all patients admitted to an intensive coronary care unit from January 2011 to March 2012, in a university hospital, in Porto, Portugal, patients with both acute myocardial infarction and diabetes mellitus were identified. A patient was considered to have diabetes mellitus if anti-diabetic therapy was being taken, if the diagnosis had been previously established on the basis of then current recommendations or if glycated hemoglobin greater than 6.5% was present at admission. Acute myocardial infarction was diagnosed following the recommendations in use. Patients with in-hospital acute myocardial infarction were excluded. Patients who were initially admitted to another hospital, and who were later transferred into our institution, were only included if the peak value for plasma troponin I could be clearly identified.

From the electronic files, the following data were obtained: age; gender; peak plasma cardiac troponin I levels; creatinine plasma levels at admission; presence of ST segment elevation in the electrocardiogram; previous history of myocardial infarction; previous coronary revascularization, either percutaneous or surgical; primary coronary angioplasty in the current episode. Troponin I was measured using the ARCHITECT STAT system, of Abbott Diagnostics (Abbott Park, IL, USA). The 99th percentile of troponin I in a normal population with this assay was established at 0.012 ng/ml.

The survival of patients was established by the retrospective study of electronic health records, after a minimum period of 36 months had passed from each admission. In the case of dead patients, the date of death was recorded, when available, or alternatively the date of the last observation of each patient. In the case of patients not known to be dead, censoring was carried out in the date of the last observation. No attempt was made to study the causes of death or the medication in use after hospital discharge.

For each class of anti-diabetic drug – insulin, metformin, sulfonylureas and DPP-4 inhibitors – patients under each of these classes of drugs were compared to the remaining patients.

Kaplan–Meier study was carried out. The comparison between groups was made using the log-rank test. Cox-proportional hazards survival modeling was used. Covariates included gender, age, plasma creatinine, peak plasma troponin I, presence of ST segment elevation, and use of each of the 4 classes of anti-diabetic drugs mentioned above.

A significance level of 0.05 was considered statistically significant. Data analysis was performed using the SPSS 22 software program, from IBM (Amonk, NY, USA). The present protocol was approved by the ethics committee of our institution.

Results

Data from a total number of 195 admissions corresponding to different patients were under analysis, out of an initial number of 954 patients admitted in the period under study, from which 200 admissions corresponded to diabetic patients (in the case of more than one admission for the same patient, only the initial admission was considered). 126 patients were of the male sex and 69 were female. The mean age was 67.6 ± 10.6 years.

ST segment elevation myocardial infarction was present in 62 patients. Primary coronary angioplasty was carried out in 44 patients. The mean peak plasma cardiac troponin I values for the 200 admissions was 49.5 ± 95.9 ng/ml.

After a period not inferior to 36 months and up to 52 months after each admission, the retrospective analysis of electronic records showed that 58 of the 195 patients had died (29.7%).

Most patients were taking at admission, alone or in combination, metformin, insulin, sulfonylureas and DPP-4 inhibitors. Thirty one patients were taking no antidiabetic therapy at admission. Nineteen patients were taking oral antidiabetic drugs, but it was impossible to establish which drugs were in use (either the patients did not recall the names of the drugs in use or the record was incomplete). DPP4-inhibitor drugs (either vildagliptin or sitagliptin) were used at admission by 35 patients, 32 of whom were also using metformin. Kaplan–Meier analysis showed that the use of DPP4-inhibitor drugs at admission was not associated to a significant change in survival, when compared to patients not taking that type of drugs, with a significance level in log-rank test of 0.957 (Fig. 1).

Concerning the other three other major types of antidiabetic drugs used by the patients, insulin (Fig. 2), metformin (Fig. 3) and sulfonylureas (Fig. 4), significant differences were also not seen in Kaplan–Meier analysis, however non-significant trends were seen in the direction of increased mortality with the use of insulin (n = 51 patients; significance level in log-rank test of 0.074) and of sulfonylureas (n = 51 patients; significance level in log-rank test of 0.167) at admission, whereas the opposite was seen with metformin (n = 92 patients) respectively.
patients; significance level in log-rank test of 0.135), in each case when compared to patients not taking the given type of drugs.

Cox analysis showed that peak plasma troponin I, age and plasma creatinine at admission were independent predictors of mortality (Table 1). On the contrary, gender, presence of ST-segment elevation in the electrocardiogram, and the use of either

DPP-4 inhibitors, insulin, metformin or sulfonylureas at admission were not predictors of mortality (Table 1).

**Discussion**

In the present report, survival of patients admitted for acute myocardial infarction was studied, according to the type of antidiabetic drugs in use at admission. The evaluation was made retrospectively, after a period not inferior to 36 months, and up to 52 months, had passed since admission. Four different types of anti-diabetic therapy were under study: metformin, insulin, sulfonylureas and DPP-4 inhibitors.

No attempt was made to evaluate the anti-diabetic therapy used by the patients after hospital discharge, however the standard policy at our institution was to use insulin (adjusted to plasma glucose) during the in-hospital stay, returning to the previous anti-diabetic therapy at discharge, except in cases previously not treated or with markedly elevated plasma glucose/glycated hemoglobin. It is therefore probable that a significant degree of overlap exists between anti-diabetic drugs used at admission and after discharge (especially in the case of patients treated with insulin). Any effect that might be observed could be due to: effects of anti-diabetic therapy during the index acute myocardial infarction episode; effects from further anti-diabetic treatment after discharge; indication bias, with a differential use of different types of anti-diabetic drugs in patients with different clinical condition (insulin being predominantly used in patients with long-standing disease). Standard therapy for these patients at discharge included double antiplatelet therapy and a statin.

Metformin use at admission was associated to a non-significant trend toward increased survival. This is not unexpected, since a consensus exists that metformin is one of the anti-diabetic drugs with the most favorable profile. Given, namely, the data reported in the “overweight” study from the United Kingdom Prospective Diabetes Study (UKPDS 34). Metformin was otherwise shown to be associated to a survival benefit in patients with incident cancer, both in comparison with other anti-diabetic drugs and in comparison with a nondiabetic population.

Insulin use at admission was associated to a non-significant trend toward decreased survival. This likely reflects, at least in part, a possible indication bias, since insulin is currently used is patients with long-standing Diabetes mellitus, often with end-organ disease. In the Outcome Reduction with an Initial Glargine Intervention study, rates of incident cardiovascular outcomes were in fact similar in the insulin-glargine and standard-care groups.

Sulfonylureas use at admission was also associated to a non-significant trend toward decreased survival. Sulfonylureas may not alter mortality of diabetic patients, when compared to metformin therapy. Sulfonylureas may interact with myocardial ATP-sensitive potassium channels; these drugs were noted to be associated with an increased risk of in-hospital mortality among diabetic patients undergoing coronary angioplasty for acute myocardial infarction. It is however possible that different sulfonylureas elicit different cardiovascular effects. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation study, the use of gliclazide was associated to a decrease in nephropathy.

Experimental data point in the direction of a favorable effect of DPP4 inhibition on infarct size. In a previous study, we failed to show any difference in peak plasma troponin levels when patients either treated or not treated with DPP4 inhibitors at admission were compared. In the present study, the use of DPP-4 inhibitor drugs at admission was notably devoid of any association to a difference in survival, since the Kaplan–Meier curves for patients either taking or not taking this type of drugs were nearly identical. This pattern is remarkably similar to what has been reported in the

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**Table 1**

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<th>Parameter</th>
<th>Significance level</th>
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<td>Peak troponin I plasma level</td>
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Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study, but the present data were obtained in a “real-world” situation, and not in the context of a controlled clinical trial, meaning that the whole range of patients was under analysis. In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care study, diabetic patients with a recent acute coronary syndrome did not have different rates of major adverse cardiovascular events if treated with alogliptin, as compared with placebo.

Study limitations – The present study has significant limitations: it is a retrospective study; the small dimension of the sample limits the strength of conclusions; no attempt was made to characterize the drugs in use after the admission or the causes of death.

Conclusions

In conclusion, the use of DPP-4 inhibitors at admission, in patients with Diabetes mellitus admitted for acute myocardial infarction, was not associated to a different survival after no less than 36 months and up to 52 months after admission.

Conflict of interest

None declared.

References

Adherence to the Mediterranean diet in children: Is it associated with economic cost?

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Objective: To assess how the diet cost is associated with socio-demographic factors and adherence to Mediterranean diet in children.

Methods: Data were obtained from a community-based survey of children selected from public elementary schools in Portugal. Of a total of 586 children attending these schools, 464 (6–12 years), were studied. Dietary intake was assessed by a 24 hour recall and the adherence to Mediterranean diet was evaluated through the KIDMED index. The cost of the diet was calculated based on the collection of food prices of a national leader supermarket, and expressed as Total Daily Cost (TDC) and Total Daily Cost-Adjusted for Energy (TDEC). Anthropometric measures were taken and socio-demographic data were gathered from a questionnaire filled by parents. Logistic regression was used to quantify the association between diet cost, socio-demographics and adherence to Mediterranean diet.

Results: The average TDC was 4.58 (SD = 1.24). Most children (69.1%) reported medium adherence to Mediterranean diet, and 4.6% rated the higher score. TDC was higher for children with highest adherence to Mediterranean diet, compared to those with lowest adherence [TDC: OR = 5.70 (95% CI 1.53, 21.33), p for trend = 0.001; TDEC: OR = 2.83 (95% CI 0.89, 8.96, p for trend 0.018)]. No meaningful variation in the diet cost with age and parental education was observed.

Conclusion: Higher adherence to Mediterranean diet was associated with higher diet cost in children.

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Introduction

The Mediterranean Diet has been object of study since the 1950s1 and is nowadays recognized for its numerous health benefits, namely protection against weight gain, obesity and diabetes mellitus type 2, cardiovascular diseases, certain tumors and other oxidative stress-related diseases.2,3

However, its original defining-characteristics do not fully correspond to the diet practiced nowadays among populations living in the Mediterranean region.4 This dietary pattern was firstly characterized by a high consumption of fruits, vegetables and grains; moderate consumption of dairy products and wine and low consumption (and amount) of red meat. Olive oil would be the main source of dietary lipids.1 Regrettably, this dietary pattern is being replaced by unhealthier choices,5,6 similarly to what is happening around the world. A low consumption of fruits and vegetables7 parallel to a growing consumption of high-density energy foods – such as snacks, sugar-rich food, fast food and soft drinks – is well documented and associated with lifestyle changes.8 These dietary modifications contribute to poorer diet quality and have been indicted as a significant explanation for the rising obesity rates, specially concerning in children.8 The same phenomenon has been also documented in Portugal.9
Changes in the physical environment and food supply have been pointed recently as major causes of the Obesity epidemic, which is becoming to be perceived from an economic perspective. In fact, substantial research on diet cost has been performed in recent years in the U.S.A. and some European countries. The results consistently show that the cost of food is a primary determinant of food choices and that higher energy density foods, which are less nutrient-rich, are associated with lower prices. On the other hand, low-energy-dense foods such as fruits and vegetables appear to be more expensive. In this context, healthier diets are associated with higher costs.

Taking into account the benefits of the Mediterranean diet, its health promoter potential, as well as the importance of price as food choice determinant, we aimed to estimate the cost of children’s diet according to the degree of adherence to Mediterranean diet. To the best of our knowledge, this is one of the first European studies on this topic in children, which may provide new information to health professionals and policy makers so they can better educate and act toward the availability of healthy eating at low cost to the common citizen. The objectives of this study were to estimate the daily cost of diet and to quantify its association with socio-demographic factors and the degree of adherence to the Mediterranean diet in children.

Methods

Participants

The data were derived from a community-based survey of children selected from 7 of the eighty public elementary schools in the city of Guimarães, Portugal, between October 2007 and March 2008. Letters were distributed to all parents or guardians outlining the aims of the study along with a consent form. From the total of 586 children attending these schools, 464 (225 boys and 239 girls) between 6 and 12 years accepted to participate in the study. Anthropometric measurements and dietary data were collected from all consenting children and questionnaires surveying sociodemographics and lifestyle information were distributed among parents or educational guardians, of which 405 have answered (87%).

The study was approved by the University of Porto Ethics Committee, the schools where the study was carried out and the Portuguese Data Protection Authority (CNPD-Comissão Nacional de Protecção de Dados, process number 7613/2008).

Assessments

Height and weight were measured by previously trained health professionals or students, following international standardized procedures. Children wore light indoor clothing and were barefooted. Weight was measured in an electronic scale, with an error of ±100 g (Seca®, Model 703, Germany), and height was measured using a stadiometer, with the head in the Frankfort plane. BMI was calculated as weight (kg)/height^2 (m)^2 and children’s weight status was categorized using the IOTF criteria and cut-points for BMI, defined specifically for sex and age. Only three categories were considered in analysis of results: normal, overweight and obesity.

Dietary intake information was assessed by a 24 hour recall, in which children were asked to recall all food and beverages consumed in the previous 24 h. A photographic manual of portion sizes and household measures (Manual of Food Quantification) was used as an auxiliary tool to estimate sizes of foods and beverages consumed.

KIDMED index was applied to verify the adherence level to the Mediterranean diet. This index was created according to the Mediterranean diet principles and provides a score ranging from 0 to 12 according 16 questions. Questions denoting a negative connotation with respect to the Mediterranean diet were assigned a value of −1 and those with a positive aspect, +1. This score was applied according to the food consumption in the previous 24 h, as described in Table 1. In accordance with the sum obtained, 3 classes were created: >8, high adherence to the Mediterranean diet; 4–7, medium adherence to the Mediterranean diet and ≤3, low adherence to the Mediterranean diet (Table 1).

The socioeconomic information and family characteristics were collected from the survey distributed to the parents or educational guardians. It contained questions about gender and age of children and parents’ education, recorded in five categories of years: 0, 1–4, 5–9, 10–12, and more than 12 years of formal education. This information was further grouped for analysis into four categories: up to 5 years, between 5 and 9 years, 10–12 years and more than 12 years of education.

Estimation of diet cost

The estimation of diet cost was divided in two tasks. Firstly, the collection of food prices, that took place between March and April of 2011. The source was an online supermarket, belonging to a Portuguese leader supermarket chain. Price data was obtained by gathering mean prices of correspondent food or package size, as well as the price per kilogram. Measurements were taken on regular prices, excluding discounts. In the case of composed dishes, diet costs were calculated using recipes available in Food Processor Plus® database (most of them previously adapted from traditional Portuguese recipes) and from a Portuguese website of traditional recipes. The price of the drinking water was estimated by the median price per gram was computed. For example, the price of rice was obtained by calculating the median of the prices of the various brands and types available in the supermarket webpage. The choice for using the median rather than the average price was based on the fact that it better represents the central values, minimizing the effect of the very high and very low prices for each group. Finally, the cost of each meal was calculated according to the contribution of each and every food ingredient taking into account its proportion.

At dietary level, two variables were created: “Total daily cost” (TDC), representing the cost of each individual’s diet and obtained by summing the cost of each meal, and “Total daily cost adjusted for energy” (TDEC) which eliminated the possible differences in

<table>
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<td>Kidmed index used to access the adherence to the Mediterranean diet.</td>
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costs associated with different energetic intake between individuals. TDEC was computed dividing TDC by the energy consumed (€/kcal) and expressed as €/1000 kcal, in order to point differences not seen with TDC.

### Statistical analysis

The statistical analyses were performed using the software Statistical Package for the Social Sciences (SPSS), version 17.0. Descriptive statistics were used to characterize the sample (mean and standard deviations). A total of 342 subjects for whom assessment of overall dietary intake was available were considered for data analysis.

Unconditional binary logistic regression models were fitted to estimate the magnitude of the association between diet cost (considering two categories, using the median value as the cut-off) and socio-demographic characteristics (sex, age and parents education) and the degree of adherence to the Mediterranean Diet (Kidmed score).

### Results

#### Participant characterization

In this sample of 464 children (51.5% girls), the prevalence of overweight and obesity were 23.3% and 7.3%, respectively. Approximately two-thirds of the study population had parents with less than 10 years of formal education. The majority of children reported a medium adherence level to Mediterranean diet (69.1%), and only 4.6% rated a higher adherence score (Table 2).

#### Diet cost

The average (±standard deviation) TDC was 4.58 (±1.24) € and the average TDEC was 2.17 (±0.42) €/1000 kcal (Table 3). No meaningful differences were observed between gender, age or parental education regarding TDC and TDEC. Accordingly, no meaningful or consistent variation in the diet cost with age and parents’ education was observed (Table 3). Concerning Kidmed score, it is noticeable an increasing in the cost of the diet with increasing level of adherence to the Mediterranean Diet (TDC of 4.79€ in high adherence category vs. 4.09€ in low adherence category, p = 0.471; TDEC of 2.19€/1000 kcal in high adherence category vs. 2.10€/1000 kcal in low adherence category, p = 0.047). Considering children reporting the higher adherence to Mediterranean diet in comparison with those with the lowest adherence, the odds favoring higher diet cost was 5.70 (95% CI 1.53–21.33, p for trend = 0.001) for TDC and 2.83 (95% CI 0.89–8.96, p for trend = 0.018) for TDEC (Table 3).

### Discussion

The present study showed that a higher adherence to the Mediterranean diet was associated with higher diet cost. The average TDC found in this sample of school-aged children was 4.58€. As far as we know, only few studies have focused on the estimation of diet cost among children. In a study conducted within a Spanish sample aged 2–24 years, researchers reported a mean daily diet cost of 3.16€ (data collected in the year 2000) and, more recently, two studies conducted within the DONALD cohort study, which includes German children, found daily diet costs also close to 3€. Studies among adults in Europe and US, reported average prices higher than 5€.

One out every twenty children in this study reported high adherence level to the Mediterranean dietary pattern, results that are in line with previous studies in Mediterranean countries. The explored relationship between diet cost and adherence to the Mediterranean diet has brought interesting results, as it was verified an increasing cost with a higher adherence to Mediterranean diet. A similar study in Spanish youth (participants were aged between 2 and 24 years) has found similar results. In literature, much has already been discussed on the higher cost of healthy diets of which Mediterranean diet is a good example. There are a few pointed aspects underlying this phenomenon, which are important to refer. The first is the content in energy dense foods that, apparently cheapen the diet, association that has already been demonstrated in the current sample of school-aged children. In another study, Rydén et al. verified higher cost of diet associated with its healthiness (assessed using the Healthy Eating Index), in which energy-density was low. Secondly, variety, a characteristic of healthy dietary patterns, is associated with a large number of food groups and foods among groups. Hence, and according to the literature, healthier groups are associated with higher costs, making the diet more expensive. In accordance to our results, food items that play an important role in the Mediterranean diet such as fruits and vegetables, but also fish, were associated to higher costs in different studies. Moreover, the contribution of healthier options within the latter group, such as lean meats and low-fat products, was further associated in the current study with an increased cost. Data in the literature relates higher costs and healthier options within the same food group. However, when analyzing Mediterranean diet in this perspective, Drewnowski et al. stated that not all nutrient-rich foods necessarily cost more and so, it should be possible to construct a Mediterranean-style diet using the lower cost options in every category.

A possible consequence of higher cost of healthy diets, such as the Mediterranean, is the higher prevalence of poor quality meals within low socioeconomic position (SEP) families, who cannot afford to spend much of the family budget on healthy foods. A study conducted in Portugal in 2006 by Moreira et al. showed that a higher education was positively linked to a better dietary quality, represented by a higher frequency of milk, vegetable soup, vegetables, fruit and fish consumption, all of which are commonly consumed within the Mediterranean pattern. The three most common SEP indicators are education, occupation and income. However, in the present study, only parental education was evaluated, and no significant association with diet cost was found. A
subsequent study covering disposable family income could add a vital step to overcome this limitation, as it was described as a better SEP marker with regard to food budget choice by Rydén et al.31

Some methodological limitations are worth noting. First, dietary intake and cost estimates were derived from a 24 h recall. The use of this instrument may have compromised the collected information, since it has been recognized that children younger than 8 years-old may not accurately recall foods and estimate portion sizes.36 Nevertheless, only approximately a quarter of our sample was younger than 8 years-old. In addition, single 24 h recall may not represent the usual dietary intake and may fail to include foods and beverages that are either forgotten or consumed infrequently, influencing the KIDMED score. As most participants were not able to detail the ingredients of the recipes (and the fat used for cooking, especially concerning for the item “dairy includes olive oil”), some assumptions were made, based on traditional Portuguese recipes. However, this fact may be diluted as a whole, given the sample size.

Second, the food price collection was basing only in one source, which may have been minimized by the fact that the supermarket chain where the prices were collected has the largest share of food market in Portugal. Also, food prices were collected three years after the dietary survey was conducted, and some changes might have occurred in that period. However, this fact is mitigated by the expectation that prices have varied in a similar way, since the Value Added Tax has not changed during the period elapsed. In addition, the seasonal variability of fresh foods production, namely fruits and vegetables, may have compromised the accuracy of the prices collected, due to the fact that food prices were gathered in a different season of the survey. Nevertheless, it is expected that, in all seasons, the prices of fresh products whose production is seasonally variable, vary so that the rise in some prices is offset by a decline of others. In turn, energy dense foods are the most resistant to inflation.14 In some cases, a lack of details about food consumed determined the need to use average values (grouping fresh and tanned foods, for instance). The use of the average price does not capture differences between brand foods and consequently underestimate the variability of food prices and of the costs associated with individual food consumption,37 which may contribute to explain the lack of association between diet cost and parental education. Furthermore, since the current study has a cross-sectional design, we are limited to demonstrate associations and the direction of these associations.

Nevertheless, this was an original study that brought important insight into dietary costs of children and its association with socio-demographics and adherence to Mediterranean diet, a topic becoming significant in terms of Public Health nutrition worldwide, especially given the economic crisis that has settled in Europe and Mediterranean countries. As food price is becoming a primary determinant of food choice, this new information should concern and be considered by nutritional health care providers and public health authorities. Nutritional education and promotion of healthy eating should be provided in a cost effective manner.

Conflict of interests

There were no conflicts of interest declared.

Author’s contribution

GA, PM and PP designed the study; GA, PM, RR, AA, VT, RB, OL, AM and PP conducted the study; RR, AA and OL collected the data; GA, PM, VT and PP analyzed the data; GA and PP wrote the manuscript. All authors read and approved the final manuscript.
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Introduction

Acute patellofemoral dislocation is the most common acute knee disorder in skeletally immature patients. In this group, the incidence of patellofemoral dislocation is approximately 43 per 100,000 individuals. After a first episode, 33% of patients continue to feel pain or a feeling of the knee giving-way; these substantially impair the physical performance of patients. Previous studies report redislocation rates ranging from 15 to 44% following a first-time dislocation. After a first-time patellar dislocation and in the absence of associated injuries such as an osteochondral fracture, an avulsion of the vastus medialis obliquus or a meniscal tear, nonoperative treatment is recommended. The most common indications for surgical treatment are failure to improve with physical rehabilitation and repeat dislocations. Multiple surgical techniques have been described in order to solve instability, regarding its multifactorial pathoanatomy. The surgical approach must be individualized for each patient and may address all contributing factors; therefore, no single surgical technique corrects all problems. Surgical options for individuals with open physes include (1) proximal realignment, (2) distal realignment, (3) lateral release, (4) medial patellofemoral ligament (MPFL) reconstruction, (5) guided growth with tension-band plates, or a combination of the procedures. Osteotomies of the proximal part of the tibia and the distal end of the femur are not indicated in this age group because of the risk for damage to growth areas and axial deviations.
Conlan et al. performed a biomechanical study of the relative contributions of the medial soft-tissue restraints in the prevention of lateral displacement of the patella. They found MPFL (Fig. 1) to be the major medial soft-tissue stabilizer, providing 53% of the total restraining force. Surgical treatment of patellofemoral instability in skeletally immature patients is evolving from non-anatomic extensor mechanism procedures to anatomic restorative procedures based on MPFL reconstruction. Nonetheless, the treatment remains controversial and long-term results are unclear, particularly in patients with associated factors such as trochlear dysplasia or patella alta when MPFL reconstruction is the sole method used to treat patellofemoral instability. Our aim was to evaluate: (1) the long-term results of MPFL reconstruction as the sole method of patellofemoral instability treatment in skeletally immature patients and (2) their relationship with the presence of other potentially associated factors.

Patients and methods

Inclusion/exclusion criteria

Our inclusion criteria were (1) patients without physeal closure (according to their X-rays which were evaluated by a senior orthopaedic surgeon and a senior radiologist), (2) patients undergoing MPFL reconstruction for treatment of symptomatic patellofemoral instability refractory to conservative treatment, (3) patients who underwent surgery with the same technique and (4) patients admitted to the same institution between 2002 and 2009 for surgery. Patients with other pathological associated conditions of the knee were excluded.

Study type

We conducted a prospective study. Patients were evaluated in the medium- (mean 44 months) and long-term (mean 116.4 months) post-operative period. The following pre-operative data were collected for each patient: (1) age, (2) gender, (3) patellar tilt, (4) patella height, (5) TT-TG and (6) trochlear dysplasia. Existing risk factors for patellofemoral instability were depicted using conventional radiographs and computed tomography. Patella height was determined using X-rays with the Caton-Deschamps index. Although the Caton-Deschamps index was first described in adults, studies evaluating the validity of the index to investigate patellar height showed that it is a simple and reliable index for evaluating patellar height in children as well. According to Théveni-Lemoine et al., the mean ± standard deviation patellar length was 33.39 ± 7.4 mm, the mean patellar tendon length was 34.57 ± 6.7 mm and the mean Caton-Deschamps index was 1.06 ± 0.21. The latter was considered in this study as the standard value. Patellar tilt and TT-TG distance were evaluated using the computed tomography. TT-TG values greater than 20 mm were considered abnormal. Trochlear dysplasia was evaluated according to Dejour et al. The patients were systematically examined arthroscopically and subsequently treated with MPFL reconstruction using a gracilis tendon autograft. The clinical results were calculated using an objective knee score according to Kujala. Additionally, the patient’s levels of physical activity were determined as per Tegner. The results were compared pre- and post-operatively (at the medium- and long-term follow-up).

Surgical technique

All selected patients underwent MPFL reconstruction (Figs. 2–4) as described by Chassaing. This is a technique for patellar stabilization by reconstruction of the medial patellofemoral ligament with the gracilis tendon. The tendon is anchored posteriorly on the soft tissue of the medial femoral epicondyle and anteriorly on the medial border of the patella. The plasty is completed by suture of the medial patellar wing.
Fig. 4. MPFL reconstruction as described by Chassaing – magnetic resonance image.

### Statistical analysis

Statistical analysis was performed using SPSS® statistics software 20. The data are depicted as mean ± standard deviation for each variable. Student’s t-test was used to compare the pre-operative and post-operative results. A significance level of $p < 0.05$ was considered.

### Rehabilitation

After repair of the ligament, the patient’s knee was kept in removable immobilizers for three weeks. Early rehabilitation protocols were used in all cases.

### Postoperative instability recurrence

The patients were divided into three groups according to patellofemoral instability recurrence after surgery:

1. Dislocation, which indicated that the patient had a total loss of congruence between the patella and trochlea;
2. Unstable, which indicated that the patient’s knee presented with a positive apprehension test or showed signs of subluxation but without a dislocation recurrence;
3. Stable, which indicated that the patient’s knee did not show a positive Smillie test or showed signs of episodes of subluxation.

### Ethics

All patients and legal guardians gave their informed written consent for follow-up evaluation and data publication.

### Results

#### Population characterization

Thirty-five patients met the inclusion criteria. There were 24 women and 11 men with a mean age of 15.9 years (ranging from 14 to 17) at the time of surgery. On physical examination, all patients presented with a clinical patellar tilt. High patella was found in 10% of patients. The TT-TG was within a normal range ($12 ± 5$ mm) for all patients. Trochlear dysplasia was observed in 80% of patients: 40% had Dejour’s type A; 34% type B; 20% type C and 6% type D.

### Functional evaluation

After the application of the Kujala questionnaire, we found a pre-operative mean score of $54 ± 11$ points. The medium-term Kujala score ($84 ± 9$) significantly improved ($p < 0.0001$) compared to the pre-operative score (preliminary results presented by Simões and Oliveira at the 11th European Federation of National Associations of Orthopaedics and Traumatology congress). However, there was a decline in the long-term ($78 ± 3$) score from the medium-term score. The Tegner activity score showed a significant decrease ($p < 0.0001$) from the pre-operative period (level $7 ± 2$) to the medium- (level $6 ± 2$) and the long-term (level $4 ± 3$) follow-up (Figs. 5 and 6). The long-term results were significantly ($p < 0.0001$) lower in the presence of trochlear dysplasia type B to D. No correlation with the presence of high patella was observed. The presence of intra-operative chondral lesions correlated with lower scores, though this was not statistically significant.

### Complications

There were three minor complications: two hematomas and one superficial infection that resolved without complications. Five patients maintained residual anterior knee pain as result of patellar chondropathy that was diagnosed intra-operatively. Three patients complained of graft donor site pain, while one patient presented with a patellar dislocation three years after surgery and three patients presented a positive apprehension test or showed signs of subluxation but without a redislocation. Knee stiffness was not observed in any patient.

### Table

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<tr>
<td>Long term (9.7 years)</td>
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**Fig. 5. Kujala and Tegner score.**

**Fig. 6. Kujala and Tegner score.**
Discussion

There are many studies analysing the results of MPFL reconstruction in recurrent patellar instability. However, most are small case series, with less than 30 patients. With the exception of studies that include a long follow-up period, such as those of Li et al.15 and Zaffagnini et al.,16 both with a six year follow-up, all of the remaining studies have short follow-ups. The majority of the studies employ adjunctive techniques other than MPFL reconstruction, making it difficult to distinguish the determining factors in their outcomes. Furthermore, many of them include skeletally mature patients. Since patellofemoral instability is a common condition among patients with open physes and many surgical techniques are not appropriate for this patient subgroup, there is a clear demand for large studies analysing the long-term results of MPFL reconstruction as the sole method of patellofemoral instability treatment. We present a series of 35 cases evaluated in the medium- (mean 44 months) and long-term (mean 116.4 months) post-operative period. Our study includes 22 women and 11 men with a mean age of 15.9 years at the time of surgery. Epidemiologically, these data are in agreement with the literature, which suggest that recurrent instability is particularly high in females from 10 to 17 years of age. According to systematic reviews on the reconstruction of the MPFL, despite the identification of several methodological weaknesses, the existing studies document good results after MPFL reconstruction alone, even in the presence of other contributing factors for the disease.17–19 Our work confirms the good results in the medium-term but shows possible long-term deterioration. Compared to the pre-operative Kujala score (54 ± 11 points), the scores remained significantly favourable in both the medium- (84 ± 9) and long-term (78 ± 3), though a decline over time was observed. The Tegner activity score showed a significant decrease (p < 0.0001) over the entire follow-up period. We found that these long-term results were significantly (p < 0.0001) lower in patients with trochlear dysplasia type B to D. No correlation with the presence of high patella was found. The presence of intra-operative chondral lesions correlated with lower scores, though not statistically significant. Trochlear dysplasia is characterized by abnormal trochlear morphology and a shallow groove. It is associated with recurrent patellar dislocation, but it is unclear whether dysplasia is congenital, the result of lateral tracking and chronic instability, or caused by a combination of factors. Trochlear dysplasia is estimated to occur in less than 2% of the population; however, it is present in up to 85% of patients with recurrent patellar instability. Dejour and Le Cotent reported that 96% of patients with a history of patellofemoral dislocation had radiographic evidence of trochlear dysplasia.20 In our study, trochlear dysplasia was found in 80% of patients. The presence of the long term deterioration especially with trochlear dysplasia in our patients may be explained by the occurrence of patellofemoral chondral lesions by repetitive trauma of a more fixed patella on a flat or convex trochlea. The long-term deterioration may also be explained by the fact that we are comparing results from patients with 10 years of difference, between young people in pubertal age with high physical activity and adults who do not have the same number of hours available for physical activity. According to the literature, the most reported complications after MPFL reconstruction include patellofemoral arthrofibrosis, graft impingement, graft failure, quadriiceps dysfunction and decreased knee range of motion. We recorded five cases of residual anterior knee pain as result of patellar chondropathy that was diagnosed intra-operatively, one case of patellar dislocation (three years after surgery) and three cases presenting a positive apprehension test or showing signs of subluxation but without a redislocation. This represents a redislocation rate of 2.85% and a residual instability rate of 11%. Quadriiceps dysfunction or knee stiffness was not observed in any patient. A decade after isolated MPFL reconstruction, results remain satisfactory. The technique presented in this study allowed for good clinical results, with few complications, using a small incision to reconstruct in an isometric fashion this important patellar stabilizer, the MPFL. However, our study draws attention to a possible functional deterioration over time, especially in the presence of trochlear dysplasia, types B to D. This subgroup, especially individuals with high physical demands, may benefit from associate trochleoplasty in a second intervention. In this context, we must remember that patellofemoral instability is a multifactorial entity and when a factor is corrected, we must not ignore the problem as a whole.

Observations

Part of the results of this paper were orally presented and discussed during the 16th Congress of the European Federation of National Associations of Orthopaedics and Traumatology (EFORT), held in Prague (Czech Republic) between the 27th and the 29th of May 2015.

Conflicts of interest

The authors declare no conflicts of interest.

References

Recognition of chronic hypoxia and pre-existing foetal injury on the cardiotocography (CTG): Urgent need to think beyond the guidelines

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A B S T R A C T

Chronic utero-placental insufficiency may result in progressive hypoxia culminating in foetal decompensation and acidosis and this is termed ‘chronic’ or ‘long-standing’ hypoxia. It is essential to recognise the features of chronic hypoxia on the CTG trace so as to institute timely and appropriate action. The current guidelines may not capture a fetus who starts labour already compromised or limited in its ability to compensate for hypoxic or mechanical stresses during labour. The aim of this short review is to explore the CTG features that allow the clinician to recognise a fetus who may present with an antenatal insult such as chronic hypoxia, anaemia, infection, foetal arrhythmias and pre-existing non-hypoxic brain injury.

Introduction

A foetus exposed to hypoxic stress in labour would be expected to demonstrate a series of physiological responses to compensate for the stress so as to avoid hypoxic-ischaemic injury. The myocardium (i.e. the pump) is protected at all cost, followed by the brain and the adrenal glands (i.e. foetal central organs) at the expense of other “non-essential” organs. CTG features which reflect this compensatory mechanisms include the onset of decelerations, absence of accelerations and progressive increase in the baseline foetal heart rate secondary to the release of catecholamines (i.e. adrenaline and noradrenaline). However, if decompensation ensues, blood supply through the carotid arteries may be reduced secondary to low perfusion pressure leading to acidosis in the brain (i.e. loss of baseline foetal heart rate variability).

Chronic utero-placental insufficiency may result in progressive hypoxia culminating in foetal decompensation and acidosis and this is termed ‘chronic or ‘long-standing’ hypoxia. It is essential to recognize the features of chronic hypoxia on the CTG trace so as to institute timely and appropriate action. This is because continuation of labour may lead to intermittent and sustained compression of the umbilical cord and progressive reduction in utero-placental circulation secondary to ongoing uterine contractions. In this situation, this may lead to rapid foetal decompensation characterized by a progressive reduction in the baseline foetal heart rate culminating in a terminal bradycardia. It is also important to recognize features of pre-existing non-hypoxic foetal brain injury on the CTG trace to optimize outcomes and to facilitate counselling of parents.

The current guidelines may not capture a foetus who starts labour already compromised or limited in its ability to compensate for hypoxic or mechanical stresses during labour. The aim of this paper is to explore the CTG features that allow the clinician to recognize a foetus who may present with an antenatal insult such as chronic hypoxia, anaemia, infection, foetal arrhythmias and pre-existing, non-hypoxic brain injury.

Understanding the foetal pathophysiology during CTG interpretation

Irrespective of the guidelines used (FIGO, NICE or ACOG) there are four features that should be noted when interpreting a CTG: baseline foetal heart rate, variability, accelerations and decelerations.1–3

Baseline foetal heart rate

This is defined as the mean level of the most horizontal and less oscillatory FHR segments and is estimated in periods of 10 minutes and expressed in beats per minute (bpm). FIGO considers the normal range to be between 110 and 160 bpm.3 An increase in baseline rate above 160 bpm for more than 10 minutes is called baseline tachycardia. Common causes include maternal dehydration
or pyrexia, a catecholamine response to a gradually evolving hypoxia and, more rarely, foetal tachyarrhythmias. A baseline rate of less than 110, persisting for more than 10 minutes is called baseline bradycardia. In addition to an acute reduction in foetal oxygenation (i.e. acute profound hypoxia or hypotension), foetal bradycardias may occur with conduction defects in the heart (heart block) and sympatholytic drugs.

The baseline foetal heart rate is regulated by the autonomic nervous system. The parasympathetic system develops later and consequently preterm foetus tends to have higher baseline rates. Conversely, for a postdate foetus a lower baseline rate is to be expected. Rather than sticking blindly to “guidelines” it is important to consider what should be the normal, “expected” baseline rate for the foetus in question based on his/her gestational age. A foetal heart rate of 100 bpm persisting for more than 10 min is called a baseline bradycardia and, in the presence of normal variability, accelerations and no decelerations could be normal for a post term foetus. Conversely, a baseline rate of 160, although it is still within the “normal range” proposed by the guidelines should not be considered as normal after 40 weeks of gestation because it may be a sign of chorioamnionitis or chronic hypoxia, even in the absence of other abnormal features on the CTG trace.

Variability

This refers to the “bandwidth” reflecting the oscillation of above and below the baseline and it reflects the continuous interaction between the parasympathetic and the sympathetic autonomic nervous systems. It is classified as normal (5–25 bpm), reduced (<5 bpm) or increased (>25 bpm). The presence of normal variability gives information regarding the integrity of the autonomic nervous system. Periods of deep sleep can have reduced variability but this is unlikely to last more than 50 min and will be followed by periods of normal variability. In addition, the baseline foetal heart rate would remain stable without any increase, in cases of foetal sleep. This reassuring pattern of alternating periods of reduced variability interspersed with normal variability reflects the different foetal behavioural states and is called “cycling”. Reduced variability can be associated with drugs (CNS depressants), antenatal brain injury or hypoxia leading to anaerobic metabolism and acidosis within the central nervous system. In hypoxia developing during the process of labour, reduction of baseline variability tends to be a late phenomenon and comes preceded by decelerations and increase in the baseline foetal heart rate secondary to the release of catecholamines. However, if this process had already started in the antenatal period, a higher baseline (catecholamine surge), repetitive shallow decelerations (stimulation of chemoreceptors by metabolic acids) and reduced baseline variability (i.e. acidosis within the brain), which are hallmarks of chronic hypoxia (Fig. 1) may be observed on the CTG trace.

Accelerations

These are transient increases in the foetal heart rate of more than 15 beats from the baseline and lasting for more than 15 s and are caused by the foetal somatic nervous system activity. Therefore, they are usually associated with foetal movements and are a reassuring feature. An antenatal CTG should not be considered normal without the presence of accelerations, although its absence during late labour is of “uncertain significance”. Caution should be taken not to confuse accelerations with overshoots (reflex tachycardia following a deceleration). Moreover, the erroneous monitoring of maternal heart rate may also present with accelerations, however, these usually have greater amplitude and coincide with uterine contractions. In chronic foetal hypoxaemia secondary to placental insufficiency, the reduction in the number of FHR accelerations is associated with a reduction in skeletal muscle activity.

Decelerations

Decelerations are defined as a transient decrease of the FHR of more than 15 bpm, lasting more than 15 s. They represent a reflex response of the foetus to reduce his/her myocardial workload in response to any hypoxic or mechanical stresses and therefore, they can be secondary to cord compression, hypoxaemia, head compression or a combination of these mechanisms. Decelerations secondary to cord compression are the most commonly seen in labour, they tend to have a “V” shape with a sharp drop and sharp recovery, lasting usually less than 60 s. When in response to foetal hypoxaemia, via central and peripheral chemoreceptors, the decelerations occur “late” in relation to the contraction and tend to assume a “U” shape with a delayed recovery to the baseline. Animal studies suggested that the purpose of this response is to reduce myocardial workload and oxygen demand by lowering the foetal heart rate. Decelerations can also occur in response to head compression, starting with the onset of uterine contractions, reaching
the nadir with the peak of contraction and returning to baseline at the end of the contraction. They are benign but also rare, accounting for only about 2% of all decelerations. However, early decelerations occurring in early labour should be viewed with caution as foetal head compression at that stage is very unlikely and therefore, it is more likely that ‘shallow’ decelerations secondary to chronic hypoxia are being misclassified as ‘early’ decelerations.

Decelerations can also have overshoots (transient increase in foetal heart rate following the ascending limb of a deceleration) that should not be mistaken for accelerations. Overshoots may indicate ongoing foetal hypotension and hypoxia secondary to intense and prolonged compression of the umbilical cord.

Over the years much focus has been put on the shape of decelerations and timing in relation with the contractions, which can be difficult to ascertain, and have poor correlation with neonatal outcomes. Emphasis should be placed on the foetal response and compensation mechanisms to the decelerations and here most guidelines agree that, despite the presence of decelerations, if the baseline is stable and variability normal, the risk of foetal hypoxia is low.

**CTG patterns in chronic hypoxia and pre-existing foetal injury with case examples**

Many foetuses sustain neurological damage leading to neonatal encephalopathy secondary to causes that operate during the antenatal period. These include hypoxic, metabolic, genetic, vascular, haematological as well as inflammatory mechanisms. Although, it may be argued that in some cases neurological damage may have already occurred, it is vital to appreciate that subjecting such a foetus to repetitive umbilical cord compression and reduced utero-placental perfusion secondary to progressively increasing frequency, strength and duration of uterine contractions in labour, may potentiate the pre-existing damage or worse, cause additional neurological damage. Therefore, the timely identification of pre-existing foetal brain injury on the CTG trace would facilitate counselling of parents regarding the guarded prognosis and is likely to optimize outcomes by avoiding the additional stress of labour to a foetus limited in his/her ability to mount a successful compensatory response to hypoxic stresses during labour. The exact contribution of antenatal factors to neonatal encephalopathy remains unclear and range from 10 to 90% in different studies.

It is also important to note that not all pre-existing foetal injuries will lead to CTG abnormalities and therefore, they may never be recognized during the intrapartum period. Also, it is unclear as to the exact contribution of intrapartum hypoxic insult to the pre-existing foetal damage in the foetus in question or the magnitude of this extra injury.

**Chronic hypoxia**

A foetus who is exposed to prolonged periods of hypoxia due to placental insufficiency will adapt to the suboptimal intrauterine environment by reducing growth, redistributing the oxygenated blood to vital organs (brain, heart and adrenals) and restrict, ‘non-essential’ somatic movements and would attempt to increase the heart rate to obtain more oxygenated blood from the placenta. Failure of these compensatory mechanisms may result in hypoxia and acidosis of the foetal brain (Fig. 2).

Typically, such a foetus exposed to prolonged chronic hypoxia will present with reduced foetal movements in the antenatal period or in early labour and the CTG will show a baseline rate on the upper limit of the normal range, decreased baseline variability, with no accelerations and possibly ongoing shallow decelerations (Fig. 1). In this context, decelerations may not fulfil the guidelines criteria of more than 15 bpm drop for more than 15 s but they are still relevant.

The reduced baseline variability and reduction in foetal movements in association with intrauterine growth restriction (IUGR) and mild hypoxaemia has been shown in various studies. Also, in the foetal sheep model, foetal heart rate patterns induced by chronic foetal placental embolization show a reduction in the number of FHR accelerations and both long and short-term variability. It has been speculated that the reduction in FHR variability associated with placental insufficiency in the animal model is likely the delay in the normal maturation of the autonomic control of FHR variation and the increased baseline due to increased circulation of catecholamine. In response to chronic hypoxia the foetus tries to increase the cardiac output, mainly by increasing the heart rate, to supply the vital organs.

In chronic foetal hypoxia, although some brain damage may have already occurred, the onset of uterine contractions and resultant reduction in utero-placental circulation will increase the risk...
of hypoxic-ishaemic encephalopathy (HIE) as well as myocardial failure leading to terminal bradycardia and potential intrapartum stillbirth. This has also been studied in the animal model where a detrimental effect of pre-existing mild hypoxia on foetal outcome following repeated umbilical cord occlusions has been shown.\textsuperscript{13}

The recognition of this CTG pattern suggestive of ‘chronic hypoxia’ should prompt an immediate delivery by caesarean section, unless a spontaneous or operative vaginal delivery is imminent. In the presence of decelerations with contractions, tocolytics such as terbutaline should be considered while preparing for delivery to avoid progressive myocardial decompensation secondary to ongoing uterine contractions and resultant reduction in foetal oxygenation.

**Foetal anaemia**

Chronic foetal anaemia is a rare phenomenon in modern obstetric practice as most foetuses with anaemia are usually identified during ultrasound scan and treated in the antenatal period. It can, however, present for the first time during the intrapartum period, either because a chronic foetal anaemia has been missed or due to a sudden foetal bleeding during labour (i.e. an acute foetal blood loss). If it is recognized and timely action is taken, the prognosis for these babies is not uniformly poor.

Since the introduction of routine anti-D prophylaxis there has been a reduction in incidence of rhesus (D) isoimmunization, but other antibodies like anti-c and anti-Kel can be also implicated in foetal haemolytic disease severe enough to cause significant foetal anaemia. Foetal infection by parovirus B19 is also a recognized cause of chronic foetal anaemia. Foetal haemorrhage in labour is rare and can be secondary to feto-maternal haemorrhage (FMH) or bleeding from a ruptured vasa previa. FMH of >80 mL and >150 mL is rare and can be secondary to feto-maternal haemorrhage (FMH) or bleeding from a ruptured vasa previa. FMH of >80 mL and >150 mL is estimated to occur in 1 in 1000 deliveries and in 1 in 5000 deliveries, respectively\textsuperscript{14} and it accounts for 3.4% of all intrauterine deaths and 0.04% of all neonatal deaths.\textsuperscript{15}

Sinusoidal foetal heart rate (SHR) pattern is defined as a regular, smooth, undulating signal with amplitude of 5–15 bpm, and a frequency of 3–5 cycles per minute lasting more than 30 min with absent accelerations.\textsuperscript{1} Severe foetal anaemia can present with true sinusoidal pattern on CTG. It has also been associated with late decelerations. It was first described by Manseau et al. in 1972 in severely affected, Rhesus-sensitized, anaemic and dying foetuses, and was called ‘sinusoidal’ (SHR) because of its “sine waveform”.\textsuperscript{16} In cases of acute anaemia/hypovolaemia secondary to bleeding from vasa previa or feto-maternal haemorrhage the sinusoidal pattern is called “atypical” (Fig. 3) in view of the less smooth, saw-tooth form.\textsuperscript{1,18} This is also called the “Poole Shark Teeth” pattern.\textsuperscript{2}

The aetiology of this rare FHR pattern is still poorly understood but it is likely to represent the absence of central nervous system control over the heart. In animal studies, chemical or surgical vagotomy and arginine vasopressin infusion produced SHR pattern, thus confirming the role of autonomic nervous system dysfunction. Also a rise in arginine vasopressin levels in the blood of post haemorrhagic/anæmic foetal lamb was documented.\textsuperscript{19}

True sinusoidal pattern is typically associated with situations that cause chronic foetal anaemia or hypovolaemia: iso-immunization, massive feto-maternal haemorrhage, twin-totwin transfusion syndrome, bleeding vasa previa and foetal intracranial haemorrhage.\textsuperscript{20} It has also been documented in several high risk obstetric conditions such as diabetes, preeclampsia, amnionitis and some foetal malformations (gastrochisis, hydrocephalus, cardiac malformations).\textsuperscript{2}

Sinusoidal pattern is a sign of foetal compromise and urgent delivery or, when possible and indicated intrauterine transfusion needs to be organized. It is however important to distinguish true sinusoidal pattern from pseudo-sinusoidal heart rate patterns. These are patterns in which undulatory waveforms alternate with episodes of normal baseline variability or reactivity (Fig. 4). This pattern is not typically associated with foetal compromise and do not need any intervention. It can be seen in physiological conditions like rhythmic movements of the mouth such as thumb sucking or with the use of narcotic analgesics.

**Foetal anomalies**

The foetal heart rate is determined by the interaction between the central nervous system, the vagus nerve, and the heart. Foetal anomalies involving the brain or the heart may alter the foetal heart patterns without correlating with a hypoxic or acidotic state. The few retrospective studies evaluating the use of CTG in foetuses with congenital structural heart disease in labour did not show any characteristic foetal heart rate pattern related to specific heart defects. In case of significant foetal arrhythmias the CTG can show very specific patterns (Fig. 5). Foetuses with arrhythmias may not be able to further increase their heart rate to compensate for the hypoxic or mechanical stress of labour as any further ‘catecholamine-mediated’ increase in the heart rate may lead to rapid myocardial decompensation. Rarely, the CTG cannot be interpreted to exclude ongoing intrapartum hypoxia. In this scenario, delivery by caesarean section is recommended if the foetal cardiac rhythm abnormalities are not amenable for medical treatment.

Foetal brain injury can present with a CTG pattern similar to chronic hypoxia with reduced variability as a key marker (Fig. 6). Sinusoidal pattern has also been described in foetuses with hydrocephalus and brain haemorrhage.\textsuperscript{20} Foetuses with gastrochisis, an abdominal wall defect typically located on the right side of a normally inserted umbilical cord with bowel protruding through the defect, have an increased risk (10–15%) of intrauterine foetal death (IUD). Some authors have proposed weekly CTG monitoring from 33 weeks to reduce the risk of stillbirth.\textsuperscript{21} The typical pathological finding of the CTG is reduced variability. It has been debated whether factors other than hypoxia, for example fluid and protein loss or pressure on the bowel, could contribute to the development of pathological CTG.

Foetal intestinal volvulus is a rare life-threatening condition, associated with foetal compromise and reduced baseline variability on the CTG.\textsuperscript{22} Most reported cases presented in the early third trimester with an average of 32.5 ± 2.6 weeks.\textsuperscript{23} Typical prenatal signs of in utero volvulus are reduced foetal movements, static abdominal mass with dilated bowel loops and reduced foetal heart
Fig. 4. Pseudosinusoidal pattern. Note change to normal variability.

Fig. 5. Abnormal foetal heart rate patterns in foetal arrhythmia. Note abrupt change in baseline foetal heart rate.

Fig. 6. CTG trace in a foetus who has sustained a pre-existing brain injury: foetal stroke.
rate variability with no accelerations on CTG. It has been speculated if parasympathetic overactivity from the volvulus or foetal pain contributed to the CTG abnormalities. Delivery by caesarean section and surgical treatment should be arranged. Foetal volvulus may be complicated by bowel perforation, bowel necrosis and/or bowel atresia. Late diagnosis of volvulus contributes to high rate of morbidity and mortality.

Infection

Inflammation secondary to infection can cause direct neurologic injury and also acts synergistically with hypoxia to increase the risk of encephalopathy. Cardiotocography was not designed to detect infection and only a minority of cases (8–12%) of chorioamnionitis will present with maternal pyrexia or tachycardia. There are, however, some CTG patterns that should raise the suspicion of underlying infection. An increase on foetal heart rate without preceding decelerations cannot be attributed to compensatory mechanism of evolving hypoxia and causes such as maternal dehydration, pyrexia secondary to epidual or infection should be excluded. Again, instead of blindly applying the ‘arbitrary’ limits of normality defined by guidelines, one needs to individualize the baseline HR for the given foetus and use the same foetus as its own control.25 Comparison of the CTG trace with a previous trace may help to assess the normal baseline for the foetus in question. Also lack of cycling has been recently shown to be associated with foetal infection26 and no guidelines to date take into account this important parameter of foetal wellbeing.

Maternal pyrexia with suspected infection should be managed with paracetamol, hydration and intravenous antibiotics. Infection alone can cause neurological damage and if delivery is not eminent, if oxytocin is required to achieve progress in labour or if there are additional risk factors such as meconium or growth restriction delivery by caesarean section is recommended. This is because foetal inflammation significantly potentiates the risk of foetal neurologic injury by up to 78 fold.9

Conclusion

Current guidelines on intrapartum foetal monitoring stipulate arbitrary cut offs for baseline foetal heart rate for all babies. This may lead to midwives and obstetricians missing on going pre-existing hypoxic or non-hypoxic and inflammatory injury in a foetus after 40 weeks of gestation. This is because due to the progressive maturation of the parasympathetic nervous system, the normal baseline foetal heart rate of a foetus at 41 weeks may be 110 bpm (i.e. at the lower limit of the normal) Hence, if this foetus is exposed to a pre-existing hypoxia or an inflammation such as chorioamnionitis, the baseline foetal heart rate may increase to 150 bpm and will not cross the upper limit of ‘160 bpm’ proposed by guidelines. It is vital to remember that “one guideline box does not fit all babies” and we have proposed a ‘Foetal Monitoring Checklist’ (Table 1) to be performed at the beginning of every CTG recording to avoid the pitfalls of missing a pre-existing foetal injury.

Conflicts of interest

The authors declare no conflicts of interest.

References


Case Report

Temporary aneurysm neck balloon occlusion during percutaneous thrombin embolization of a superficial femoral artery pseudoaneurysm

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ABSTRACT

An iatrogenic pseudoaneurysm of the superficial femoral artery was embolized with ultrasonographically guided thrombin injection. In order to avoid thrombin migration to the limb arteries, during the injection, the aneurysm neck was temporarily occluded, inflating a 5 mm balloon. The balloon was deployed endovascularly with a crossover technique. At six months’ follow-up, the pseudoaneurysm remained occluded and the limb arteries were patent.

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Case report

A 79-year-old female was admitted with a pulsating mass in the right thigh. Three months before, a temporary haemodialysis catheter had been inserted in the right common femoral vein. She underwent a Doppler ultrasound which showed a right superficial femoral artery pseudoaneurysm measuring 6 cm × 5 cm with a 5 mm × 5 mm × 1 mm neck (Fig. 1). In order to plan the pseudoaneurysm correction a CT scan was performed (Fig. 2). We decided to correct the aneurysm with thrombin injection, while the aneurysm neck was occluded with a balloon. The left common femoral artery was punctured. Using a crossover technique, a 5 mm balloon was displaced at the right superficial femoral artery, near to the pseudoaneurysm neck. Percutaneous ultrasonographically guided thrombin injection was performed under real time color Doppler ultrasound monitoring. During the thrombin injection the balloon was inflated to occlude the aneurysm neck (20 min in each thrombin injection) (Fig. 3). Injection was performed as far away as possible from the pseudoaneurysm neck. There were no complications and the pseudoaneurysm was excluded. Doppler ultrasound performed six months after the treatment, showed no blood flow in the aneurysm sac and the superficial femoral artery was patent (Fig. 4). The distal right limb pulses were present.

Fig. 1. Doppler ultrasound of the right superficial femoral artery pseudoaneurysm. A typical “to-and-fro” waveform in the neck of the pseudoaneurysm is shown.

Discussion

Pseudoaneurysms are frequently iatrogenic. The pseudoaneurysms can cause skin necrosis, neuropathy, deep venous thrombosis and can rupture.1 They should be excluded to avoid these complications. They can be treated with ultrasound-guided compression, surgical intervention, stent implantation or with percutaneous thrombin injection.2,3 Due to its minimally invasiveness, percutaneous thrombin is an appealing option.2 However, in

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pseudoaneurysm with short and large neck there is a risk of thrombin embolization to the nearby artery. In the case report described, thrombin embolization could cause acute limb ischemia. To minimize this risk, during the thrombin injection, the pseudoaneurysm neck was temporarily occluded with a balloon. In the case reported this was a valuable option.

**Conflicts of interest**

The authors declare no conflicts of interest.

**References**

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