Sveriges lantbruksuniversitet
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– An investigation into current areas of development

Individualiserad nutrition

– En undersökning av hur området utvecklas

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Department of Molecular Sciences
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Abstract

Diet related diseases is an increasing problem, and new approaches are needed to prevent, motivate and treat affected individuals. Evidence show inter-individual nutrient requirements and differences in response to dietary manipulations. National dietary guidelines are generally one set of advice to the entire healthy population. While specific dietary guidelines for metabolic diseases exist, individualized preventive measures for people at risk is sought after. To meet the demands of individualization, the field of personalized nutrition (PN) is emerging which aims to create and maintain healthy dietary habits for all phenotypes without regard for their health status. This literature review examines areas of development and investigates different levels of personalization by employing information from different biological disciplines. By analyzing nutritional metabolites in plasma i.e nutritional metabolomics, it makes it possible to study the interactions between these and gut microbiota, nutrigenomics and phenotypic metabolites. By forming clusters of distinct molecular phenotypes i.e. metabotypes, it may be possible to deliver targeted dietary advice (DA) to the groups in the population with similar phenotypic characteristics through the use of metabolomics. PN has the potential to be an important tool for achieving healthy dietary habits, e.g. by predicting and identifying responders to certain dietary interventions which achieve a low postprandial glycemic response. However, current evidence does not support the eventual health benefits with including individual information in DA to the population. Integrating omics technologies and applying technical solutions e.g internet, for the distribution of DA has shown to have strong potential in delivering PN.

Keywords: personalized nutrition, metabolomics, metabotyping, nutrigenomics

Sammanfattning

Dietrelaterade sjukdomar är ett ökande problem och det eftertraktas nya sätt att förhindra, motivera och behandla berörda individer. Evidens visar på skillnader i interindividuellt näringsbehov och respons på dietära förändringar. Nationella riktlinjer för diet är oftast ett generellt råd riktad till hela den friska befolkningen. Medan specifika kostråd för metabola sjukdomar existerar, söks fortfarande individanpassade preventiva åtgärder för personer i risk. För att bemöta behovet av individualisering, har fältet med individualiserad nutrition (PN) uppstått med målet att skapa och upprätthålla hälsosamma kostvanor för alla fenotyper oberoende av hälsostatus. Den här litteraturgenomgången undersöker områden i utveckling och dess olika nivåer av personalisering genom att använda information från olika biologiska ämnesfält. Genom att analysera nutritionsmetaboliter i plasma, s.k. metabolomik, blir det möjligt att studera metaboliternas interaktioner med tarmflora, nutrigenomik och fenotypens egna metaboliter. Med hjälp av att skapa kluster bestående av distinkta molekylära fenotyper (metabotyper), skulle anpassade kostråd (DA) kunna administreras till dessa grupper i befolkningen genom användandet av metabolomik. PN har potential att bli ett betydelsefullt verktyg för att åstadkomma hälsosamma kostvanor, t.ex. genom att förutse och identifiera individers respons på dietära interventioner i syfte att uppnå låg postprandial glykemisk respons. I nuläget saknas stark evidens för hälsofördelar erhållna genom individuellt anpassade råd till populationen. Integrering av omics-teknik och tillämpning av tekniska lösningar, t.ex. internet, för distrubiton av DA har visat sig ha en stark potential för att leverera PN.

Nyckelord: Individsanpassad nutrition, metabolomik, metabotyp, nutrigenomik …

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Abbreviations

BMI	Body mass index
DA	Dietary advice
GLC	Glucose levels
HDL	High density lipoprotein
PA	Physical activity
PN	Personalized nutrition
PPGR	Postprandial glycemic response
TAGs	Triglycerides
TC	Total cholesterol

1 Introduction

National dietary guidelines are usually based on a transparent evidence-based approach, such as large scale epidemiological studies on parameters for a healthy lifestyle, which have then been validated by systematic reviews. This results in a large amount of clinical data from which dietary recommendations are aimed to the healthy population. These recommendations are set after the minimum nutrient requirement to sustain health in the population (Nordic Nutrition Recommendations, 2012). However, relationships between diet and health are complex, and detailed, personalized dietary advice (DA) has therefore been difficult to practically implement. The slow progress of the metabolic syndrome is a good example of the difficulties in studying nutrition and its effects. Also, inter-individual differences affected by demographic characteristics result in varying requirements for nutrients (Kirwan *et al.*, 2016). There is a growing body of evidence that individuals react differently to dietary provocations (Zeevi *et al.*, 2015). This indicates that the general approach with one set of DA to the entire population might be convenient, but perhaps not effective in meeting individual requirements. This is further displayed by nutrition related illnesses such as stroke and cardio vascular disease being global leading causes of death (WHO, 2017).

Today there is multiple dietary advice for different diseases, such as cardiovascular disease, diabetes, stroke, high blood pressure and other diseases related to the metabolic syndrome. For many groups, the advice is brought on by the disease itself (Livsmedelsverket, 2016). However, another interesting approach to multiple diets that is being increasingly investigated is personalized nutrition (PN). The intention with PN is to create and maintain healthy dietary patterns, for healthy and unhealthy individuals. The idea is to simplify identification of risk groups and give personalized dietary advice, and by doing so hinder further development of diet-related disease (Gibney, Walsh and Goosens, 2016).

Among the determinants of individual responses to dietary exposure, i.e. the basis for PN, are several lifestyle factors, including physical activity and diet. The

knowledge of the individual's genotype and phenotype may create other dimensions for consideration. Dietary research is complex because of the many affecting factors. In a population-based approach, dieticians can adjust dietary guidelines for the individual based on the assessment of these lifestyle factors. But the high degree of complexity may be better addressed at a personalized or intermediate group level between population and individual (O'Donovan *et al.*, 2016).

PN can be approached from different angles and personalizing approaches have been made e.g. using nutritional metabolomics, which studies interactions between diet and metabolic regulation (Rubio-Aliaga, Kochhar and Silva-Zolezzi, 2012; Zeevi *et al.*, 2015). Nutritional metabotyping is the practice where individuals are clustered according to their metabolic or phenotypic profile (Gibney and Walsh, 2013; O'Donovan *et al.*, 2015). Another aspect of diet x health interactions regards how the gut microbiota can be altered by different diets and how this, depending on the microbiome, affects the host (Sonnenburg and Bäckhed, 2016).

1.1 Aim

The aim of this thesis was to highlight the potential of PN to improve individual and population health in the form of a literature review. Specific objectives included i) to highlight important areas of development of PN in current research ii) to investigate personalization at different levels, e.g. employing information from metabolomics, genetic, microbiome, and anthropometric levels; and iii) to identify strengths and weaknesses of different areas of personalization.

2 Method

PubMed and Scopus were used to extract relevant literature. Keywords were: " "personalized (personalised) nutrition" OR "precision nutrition" " within the title and/or abstract, to identify an initial set of relevant original research studies and review articles. Through these references, further articles of interest were identified. Articles based on specific sub-populations that were not representative of the general population, e.g. pregnant women, were excluded. As this field is emerging and most studies are from this current decade, exclusion through date was not deemed necessary.

3 Fields of Personalized Nutrition

3.1 Nutritional metabolomics

Metabolomics measures small-molecule metabolites, normally in urine or plasma. In nutritional metabolomics, this methodology is used to investigate how metabolites and metabolic regulation are related to dietary intake. Metabolites are analyzed through two main approaches. In targeted metabolomics, a list of a priori selected metabolites are quantitated or semi-quantitated and there is usually a pre-determined hypothesis. The main technique is nuclear magnetic resonance (NMR) as it is a robust analytical method well adapted for accurate quantification. Untargeted analysis profiles as much as possible of the metabolome to e.g. discovering new biomarkers. Liquid chromatography mass spectrometry (LC-MS) is highly sensitive, it can detect information about the molecular structure which makes it possible to separate neighboring molecules, making it suitable to detect new metabolites (Barnett *et al.*, 2014; Mathers, 2016). It should, however, be noted that a common bottleneck in especially MS-based metabolomics is the accurate transformation of raw analytical data into accurate quantification of identified metabolites. Metabolomics analyses can also be applied on individual foods which can allow for the creation of databases of food constituents. This is relevant when examining the effects of a specific food and if there is a metabolite, or a combination of such, that is responsible for an effect. It also gives insight into the regulatory role of nutrition and thus human health, which connects to the importance of identifying disease-related nutritional metabolites (Gibney *et al.*, 2005; Barnett *et al.*, 2014).

There are already known metabolites involved in metabolic regulation that are widely used as biomarkers for both health and disease such as insulin and blood glucose for diabetes (Kohlmeier *et al.*, 2016). Through the use of metabolomics, biomarkers that reflect actual exposures to nutrients can be identified and used not

only for epidemiological risk modeling but also to predict e.g. responders to dietary interventions and thus enable the development of PN (Guertin *et al.*, 2014; Kim *et al.*, 2017).

A challenge in metabolomics is for the scientific community to decide on which metabolites are important to focus on, from the vast amount of metabolites that exists, in relation to specific research areas, such as diet x health interactions (i.e. nutrition) (Gibney *et al.*, 2005). Other challenges are the presence of non-nutrient metabolites that can interfere with results, even though these could be useful as biomarkers of exposure. Detected metabolites could also have been influenced by the gut microbiota, individual to the subject. Therefore, results could vary depending on the individuals microbial composition in addition to the dietary intake being analysed (Guertin *et al.*, 2014).

3.2 Postprandial glycemic response

It is generally accepted that maintaining stable blood glucose levels is beneficial to sustain health. Irregular blood sugar levels have been linked to the development of type II diabetes, obesity and other metabolic diseases (Grundy, 2012).

Postprandial glycemic response (PPGR) is measured by glucose monitoring after a meal and gives important information on the regulation of blood glucose (Zeevi *et al.*, 2015). New research is revealing that there is an inter-individual difference of PPGR to the same foods. In a study by Zeevi and colleagues (2015), a cohort of 800 participants had their glucose levels monitored for a week while eating standardized meals at the start of the day, in addition to their usual diet. The results revealed a large variability between individuals in PPGR to the same foods. For instance, the mean PPGR for bread in the entire cohort was 44 mg/dl*h, whereas the bottom 10% mean was 15 mg/dl*h and the corresponding top 10% was 79 mg/dl*h.

Using recorded data on e.g. dietary habits, anthropometric measurements, physical activity (PA) and gut microbiota, Zeevi and colleagues (2015) developed an algorithm to predict personalized glycemic responses to meals which was successfully validated on an external 100-person cohort. The prediction algorithm was then used to generate individualized intervention diets to regulate the PPGR for a low or a high (“good” or “bad”) response respectively on additional 26 participants. The participants followed the 2 different diets where the PPGR in the “bad” diet was notably higher than in the “good”.

Considering that elevated postprandial blood glucose levels are linked to the development of diseases such as diabetes, obesity or cardio-vascular disease, Zeevi and colleagues’ (2015) results suggest the need to differentiate the concept of

healthy foods down to the individual level in order to lower the PPGR and indicate that an algorithm can be used effectively for this purpose.

The potential of predicting foods that minimize glucose spikes is an important factor in managing disease. Future research on predicting PPGR to manage and perhaps reverse pre-diabetics is desirable. Furthermore, this promising approach relies on multivariate predictive modeling and is as such not limited to predicting PPGR, but could also be extended to other endpoints of relevance for health and wellbeing.

3.3 Gut microbiota

The human body acts as a host for thousands of gut microbial species in the gastrointestinal tracts, predominantly species belonging to *Firmicutes* and *Bacterioidetes* (Sonnenburg and Bäckhed, 2016). Studies are showing that the formation of the gut microbiome initiates in the fetus *in utero* through the exposure to the maternal microbiome in the intrauterine environment (Gohir *et al.*, 2014). The microbiome is then shaped throughout life by various influences such as vaginal birth, breast feeding, the immune system, diet, antibiotic-use and other life-style factors (Nicholson *et al.*, 2012) The microbiota exists in symbiosis with the host, living off e.g. fermentable polysaccharides, amino acids or lipids and providing metabolites for the host that are essential for health.

One such group of metabolites are the short chain fatty acids (SCFA) that were shown to have a positive effect on e.g. glucose homeostasis, blood lipids and weight maintenance (Byrne *et al.*, 2015). In a study by De Filippo and colleagues (2010), the gut microbiota of urban Italian children eating a western diet was compared with that of children from rural Burkina Faso (BF) living on a diet low in fat and animal protein and high in starch, fibers, and polysaccharides. The results showed a larger variability of the microbiome in the gut of children from rural BF, including genes from microbes that didn't exist at all in the European children. Some of these specific microbes are known to specialize in breaking down cellulose which indicates that the gut microbes utilize their potential to obtain as much energy as possible from the fiber rich food that is a major component of their diet. As a result, the BF children also had more SCFA in their stool samples and notably lower levels of *Enterobacteriaceae,* which could be a direct consequence of the higher levels of SCFA (De Filippo *et al.*, 2010). These results clearly show that the microbial composition is very much affected by the nutrients the individuals consume, which in turn have major effects on the individuals' health.

Another example of how diet can alter the microbial composition are microbes that degrade porphyran, a polysaccharide commonly found in seaweed (Nori, common in sushi), which can be found in the microbiota in populations with high levels of seaweed as part of their staple diet (Hehemann, 2010).

The previously mentioned study be Zeevi et al (2015), in addition to showing that metabolic responses (PPGR) to dietary provocations were highly heterogenous, the intervention diets also showed to have a positive effect on the gut microbiome, shifting to microbes that are associated with health (Zeevi *et al.*, 2015). The microbial composition determines the metabolites produced which in turn affect the immune system of the host and since diet affects the microbial composition, this has been shown to be an effective approach to influence human health and an important parameter to consider when forming dietary advice (Sonnenburg *et al.*, 2010; David *et al.*, 2014).

3.4 Metabotyping

The concept of metabotyping is based on identifying clusters of individuals with similar metabolic or phenotypic profiles that have similar metabolic responses to e.g. dietary exposures, as can be seen in Figure 1, which then allows targeted dietary advice to be delivered to these clusters (O'Donovan *et al.*, 2015).

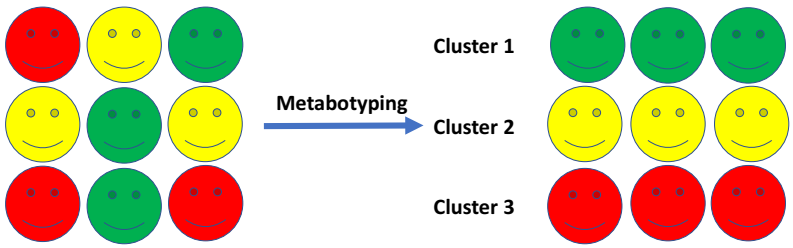

Figure 1. An overview of how metabotyping can be implemented to create clusters of individuals with similar dietary needs, based on their metabolic profile, where each colour represents a specific profile (O'Donovan *et al.*, 2015).

A study carried out on the "Irish National Adult Nutrition Survey", identified metabotypes by cluster analysis where serum samples were measured for triglycerides (TAGs), total cholesterol (TC), HDL cholesterol, and glucose levels (GLC), all metabolic markers for health. Three metabotypes were identified: cluster 1 included individuals with a markedly healthy marker profile (low TAGs, high HDL and low GLC), cluster 2 had low TC but intermediate values for the other parameters and cluster 3 had a profile indicative of poorer health status (high TAGs, low HDL, high TC and high GLC). By developing a decision tree including parameters such as BMI, waist circumference and blood pressure, personalized dietary advice could be administered. This targeted advice was then successfully validated against fully individualized advice from a dietician, highlighting the potential to develop automatized dietary advice for personalized nutrition (O'Donovan *et al.*, 2015). Using metabotyping for PN has so far not been tested clinically on a large scale. There is extremely limited data on how individuals will respond to automated advice but compliance is generally believed to be favored by personalized advice from a dietician rather than from an algorithm. However, the access to a dietitian for the individual may be scarce and the opportunities for advice and feedback may be much higher using an automated system.

3.5 Nutrigenomics

Nutrigenomics is the study of how nutrients and genes interact, i.e. how food and its constituents affect the gene expression, and also how the genetic variation affects the nutritional response to the food (Nielsen and El-Sohemy, 2012).

The focus has been on single-nucleotide polymorphisms (SNPs), i.e. the variation of a single nucleotide in an exact location in the genome, with a prevalence of > 1% in the general population, as some SNPs are associated with disease (Nature Education, 2014). This is exemplified with SNPs that can alter the metabolism, as they may affect the synthesis and function of proteins, such as individuals with phenylketonuria (PKU). These individuals have a mutation that causes decreased metabolism of the amino acid phenylalanine and avoiding foods rich in phenylalanine is required to remain healthy (Ferguson *et al.*, 2016). By altering the diet, the expression of these gene variants can be affected which can either increase or decrease the risk of disease (Mead, 2007).

SNPs associated with nutrition are amongst other MTHFR- and FTO genotypes. A study found that DA including genetic information on carrying the FTO risk allele for obesity, resulted in more weight loss for participants that carried the allele vs the participants that didn't (Celis-morales *et al.*, 2017). Another study investigated whether participants receiving information on carrying the MTHFR gene, which is

related to cardiovascular health and is mainly linked to insufficient consumption of folate, would make dietary changes and increase their folate intake. However, no changes could be observed in the individuals receiving their genetic information (Clare B O'Donovan *et al.*, 2016).

As exemplified by these two studies, there is inconsistency regarding how to interpret effects in nutrigenomics. A possible hypothesis could be that the group risking obesity might have reacted more to their genetic information as the risks of obesity are addressed daily in society, in comparison to the risks of folate insufficiency. If this inconsistency applies to the entire field of nutrigenomics is difficult to say, it does however highlight the complexity of this research.

It is important to identify SNPs and their expressions as they may be affected by diet and thus potentially modifying disease risk. Furthermore, the data that SNPs provide, point to the linkage between genotype and inter-individual nutritional requirements. A possibility could therefore be to involve techniques such as metabotyping to form the basis for targeted delivery of DA to these genetic clusters.

3.6 Personalizing dietary advice on 3 levels

To investigate if dietary advice through PN could be delivered and have a positive effect on dietary habits in comparison to traditional dietary advice, a model with three different levels which build on each other was developed (Gibney and Walsh, 2013; Celis-Morales *et al.*, 2016). Dietary advice for level 1 is based on the individuals' dietary intake, anthropometric measurements (weight, BMI) and physical activity. Level 2 is based on level 1, extended with waist circumference and phenotypic data which includes a nutrition-related blood profile consisting of glucose, total cholesterol, carotenes and omega-3 index. Level 3 is based on level 2 and genotypic data related to nutrition.

To understand if dietary advice following these levels could result in healthy dietary changes, a large-scale internet-based randomized controlled trial was conducted in seven European countries (Food4Me study). The 1607 participants were randomized into four groups; level 0 to level 3. Level 0 was the control group with non-personalized dietary recommendation and the following 3 groups received dietary advice following the levels described above (see Table 1). All the 1269 participants that completed the six month intervention improved their diet during the trial. The participants receiving a level 1-3 intervention had decreased their consumption of red meat, salt, saturated fat and overall energy intake and increased their consumption of folate in comparison to the control group. After the 6 month intervention, there were however no significant differences between the three levels of DA

and, correspondingly, no evidence of increased effect of the inclusion of phenotypic and genotypic data (Celis-Morales *et al.*, 2016).

Table 1. Personalized nutrition based on different levels of information in the Food4Me study (Celis-Morales *et al.*, 2016).

Level 0	Level 1	Level 2	Level 3
Control	Dietary intake	Dietary intake	Dietary intake
-	Anthropometric measurements (weight, BMI)	Anthropometric measurements (weight, BMI, waist circumference)	Anthropometric measurements (weight, BMI, waist circumference)
-	Physical activity	Physical activity	Physical activity
		Blood profile consisting of glucose, total cholesterol, carotenes and omega-3 index	Blood profile consisting of glucose, total cholesterol, carotenes and omega-3 index
			Genotypic Data (MTHFR, FTO, TCF7L2, APOE e4 and FADS1 genes)

Although these results indicate that the proposed levels did not result in differential dietary behavior change, the Food4Me study has presented other important results. Kirwan and colleagues (2016) investigated which phenotypic characteristics that, together with personalized DA, could affect circulating cholesterol concentration. Subjects were classified as responders or non-responders to the intervention depending on the change in cholesterol from baseline. Factors that varied and had importance if a subject would respond or not was found to be age, baseline total cholesterol, glucose, five fatty acids and alcohol intakes (Kirwan *et al.*, 2016). The ability to identify phenotypes that are responsive to DA may be vital in the process to deliver PN.

An important outcome of the Food4Me study was the successful use of internet and technology to administer the recommendations, showing a positive adherence without physical meetings. This creates opportunities to scale time and cost efficiently and reach many individuals with information.

A suggestion for a future study in this field could be to combine this technology with metabotyping instead of the levels 1-3 so individuals with similar metabotypes can be connected through a platform and e.g. create a social support system.

3.7 Content of personalized nutrition

To fully comprehend the interaction of nutrition and human health, data from the different layers of biological information mentioned above should be combined and co-analyzed.

A crucial development to translate untargeted metabolomics into applied science and clinical practice is to achieve accurate large scale identification of metabolites from raw instrument data, including also their metabolic and nutritional effects. Such identification would simplify further investigation of the interactions between metabolites and genome or microbes as these are both known to influence the effect of nutrients. For instance, nutrients can affect the microbiota and the metabolites they produce which in turn affects the host's immune system and overall health. Therefore, a database cataloging metabolites such as the "Human Metabolome Database" (www.hmdb.ca) could increase the understanding of nutritional cause and health effects (Rubio-Aliaga, Kochhar and Silva-Zolezzi, 2012).

The ability to predict and identify responders to dietary interventions is valuable for nutritional research; the use of phenotype characteristics from e.g. metabolomics was e.g. effectively used by Zeevi and colleagues (2015) to successfully predict individual PPGRs. Measuring phenotypic and to some extent genotypic characteristics were also shown to be an efficient way to create clusters of individuals with similar dietary needs and distribute DA through metabotyping, e.g. using metabolomics (Brennan, 2017).

The use of individual data obviously has distinct advantages for individuals at risk because of genetic dispositions. Although administration of PN to the general population through different levels of biological data is currently not supported by the limited evidence, personalization through metabotyping seems to have strong potential. As technology evolves, PN can become more widely available. Analyzing phenotypes and nutrient status can already be achieved from home with dried blood spots, making PN less reliant on clinics (Gibney and Walsh, 2013). In the near future, the possibility to deliver personalized DA through the internet and mobile phones could become time- and cost-effective alternatives to personalization through physical meetings with health professionals and, through a high degree of automation of instrumental and data analysis, may supply personalized advice and feedback without overburdening these professionals. This might not always be the preferred alternative as personal, qualified involvement sometimes is the best option for healthy dietary transactions (Kohlmeier *et al.*, 2016).

There are other studies that incorporate psychological determinants and environmental and social factors in the development of PN (Nordström *et al.*, 2013; Poínhos *et al.*, 2014). These essential aspects of PN are important to integrate with any further research.

4 Conclusion

Diet is a modifiable risk factor for the major cardiometabolic diseases and accurate DA is an important strategy for improved health and wellbeing for the individual as well as for society. In this review, the potential of PN to improve individual and population health was investigated.

Targeted dietary advice for the population is a step towards PN, by grouping metabotypes, with similar gut microbiome, SNPs or phenotypic characters. Such metabotypes are likely best identified through reflections in the phenotype, e.g. by the application of metabolomics. To successfully deliver PN to both individual and population, new omics technologies and the use of the internet have a strong potential.

It has become evident that there is large inter-individual variation in nutritional requirements. Therefore, there is strong potential of using personalized or group-based dietary advice with the intention of creating a healthier population. There is however a need for more research in this complex field.

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