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PLASMA METABOLOME PROFILING OF THE KAZAKHS

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Abstract

Introduction: The determination of metabotype variations can be used to predict disease risk and diagnosis, understand molecular pathophysiology, interpret the understanding of environmental and lifestyle influences, develop and evaluate drug efficacy, toxicity, and adverse reactions.

Aim: In this study metabolic differences among adults living in Kazakhstan are assessed to identify and characterize the metabolic profiles and profiles of clinical biomarkers.

Materials and Methods: Observational trans-sectional study of healthy Kazakhs. To perform the tasks, metabolom study of plasma was conducted among 74 Kazakh nationality study participants. The study was carried out on a platform based on tandem technology of ultra-high liquid chromatography and mass spectroscopy (Ultrahigh Performance Liquid Chromatography-Tandem Mass Spectroscopy (UPLC-MS / MS)). The determination of the level of biochemical indices in blood serum was performed on a biochemical analyzer Cobas 6000, Roche Diagnostics. The necessary logarithmic transformation and ANOVA variance analysis, a two-sample Welch t-test, were performed to determine the bio-compounds that differed significantly between the experimental groups.

Results: The study was conducted to gain an understanding of the metabolic changes that occur in young adults and adults over 45 years. As a result of 74 participants, 853 different biochemical indicators of the main pathways for the metabolism of amino acids, pethids, nucleotides, carbohydrates, cofactors and vitamins, xenobiotics, lipid and energy metabolism were identified.

Conclusion: The changes in several known metabolites and various prospective metabolic pathways in the group older than 45 years are found compared to a group of young people. Metabolic differences included changes in metabolites associated with the metabolism of fatty acids, steroidogenesis (steroid hormone biosynthesis), secondary carnitine metabolism, inflammation and oxidative stress.

Keywords: *metabolomics analysis, metabolites, cardiometric disorders, Kazakh population.*

Резюме

ПРОФИЛИРОВАНИЕ МЕТАБОЛОМА ПЛАЗМЫ КАЗАХОВ

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Введение: Определение вариаций различных метаболитов может применяться для прогнозирования риска заболевания и диагностики, понимания молекулярной патофизиологии, при интерпретации понимания влияния окружающей среды и образа жизни, а также при разработке и оценке эффективности лекарственных препаратов, токсичности и побочных реакций.

Цель: В данной работе проведена оценка метаболических различий среди взрослого населения, проживающего на территории Казахстана для выявления и характеристики метаболических профилей и биомаркеров.

Материалы и методы: Одномоментное транс-секционное исследование практически здоровых казахов. Для выполнения задач проводилось исследование метаболома плазмы крови у 74 участников исследования казахской национальности. Исследование проводилось на платформе по тандемной технологии сверхвысокой жидкостной хроматографии и масс-спектроскопия (Ultrahigh Performance Liquid Chromatography-Tandem Mass Spectroscopy (UPLC-MS/MS)). Проведено необходимое логарифмическое преобразование и ANOVA дисперсионный анализ, двухвыборочный t-test Уэлча для определения биосоединений, которые отличались значительно между экспериментальными группами.

Результаты: Исследование было проведено с целью получить представление о метаболических изменениях, которые происходят у молодых и взрослых лиц старше 45 лет. В результате метаболомного анализа 74 участников исследования определено 853 различных биохимических показателя основных путей метаболизма аминокислот, пептидов, нуклеотидов, углеводов, кофакторов и витаминов, ксенобиотиков, липидного и энергетического обмена.

Выводы: Обнаружены изменения нескольких известных метаболитов и метаболических путей у группы старше 45 лет по сравнению с группой молодых лиц. Метаболические различия включали изменения метаболитов, связанных с обменом жирных кислот, стероидогенезом (биосинтез стероидных гормонов), с процессами воспаления и оксидативного стресса.

***Ключевые слова**: метаболомный анализ, метаболиты, кардиометаболические нарушения, казахская популяция.*

Түйіндеме

ҚАЗАҚ АДАМДАРДЫҢ ПЛАЗМА МЕТАБОЛОМЫНЫҢ ПРОФИЛІ

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Кіріспе: Әртүрлі метаболиттердің вариациясын анықтау әдісін ауру қауіп-қатерін болжау және диагноз қою кезде, молекулярлық патофизиологияны түсіну үшін, қоршаған орта және өмір салтының ықпалын талдаған кезде, сонымен қатар дәрілік препараттарды зерттеу кезде тиімділігін, улылығын, қосымша реакцияларды бағалау үшін қолдануға болады.

Мақсаты: Осы жобада метаболиттік профильдері және биомаркердерді анықтау және сипаттау мақсатында Қазақстан территориясында тұратын ересек адамдар арасындағы метаболиттік айырмашылық бағалау орындалды.

Материалдар мен Әдістер: Зерттеу дизайны: Қазақ адамдарын бір сәтті транс-секционды бақылау. Мақсатты орындау үшін зерттеуге қатысқан 74 қазақ ұлттың өкілдерден қан плазмның метаболомға зертеу жүргізілді.Зерттеу шамадан тыс жоғары сұйық хроматография және масс-спектроскопияның (Ultrahigh Performance Liquid Chromatography-Tandem Mass Spectroscopy (UPLC-MS/MS)) тандемді технологиясы бойынша платформада өткізілді. Тәжірибелік топтар арасында айтарлықтай ерекшеленген биологиялық қосылыстарды анықтау үшін қажетті логарифмдік түрлендірулер және ANOVA дисперстік талдауы, екі таңдаулы Уэлс t-тесті өткізілді.

Нәтижелері: Зерттеу жас және 45 жастан жоғары ересек адамдарда өтетін метаболиттік өзгерістер туралы түсінік алу мақсатында өткізілді. 74 зерттеуге қатысушыларды метаболомдық талдау нәтижесінде аминқышқылдар, пептидтер, нуклеотидтер, көмірсулар, кофакторлар мен дәрумендер, ксенобиотиктер, липидтік және энергиялық алмасу бойынша негізгі метаболизм жолдарының 853 түрлі биохимиялық көрсеткіштері анықталды.

Қорытынды: 45 жастан жоғары адамдар тобында жас адамдар тобымен салыстырғанда бірнеше белгілі метаболиттер мен метаболиттік жолдарда өзгерістер анықталды. Метаболиттік айырмашылықтарға май қышқылдары алмасуымен, стероидогенезбен (стероидты гормондардың биосинтезі), қабыну үрдістері мен оксидативті стресспен байланысты өзгерістер кірді.

***Түйін сөздер**: метаболомдық талдау, метаболиттер, кардиометаболиттік зақымданулар, қазақ популяциясы.*

Библиографическая ссылка:

Абильмажинова А., Кожамкулов У., Джозеф Ли, Акильжанова А. Профилированое метаболома плазмы казахов / / Наука и Здравоохранение. 2017. №4. С. 27-37.

Abilmazhinova A., Kozhamkulov U., Joseph Lee, Akilzhanova A. Plasma metabolome profiling of the kazakhs. *Nauka i Zdravookhranenie* [Science & Healthcare]. 2017, 4, pp. 27-37.

Әбілмажинова Ә., Қожамкулов Ұ., Джозеф Ли, Ақылжанова А. Қазақ адамдардың плазма метаболомының профилі / / Ғылым және Денсаулық сақтау. 2017. №4. Б. 27-37.

Introduction

Metabolom is a collection of all metabolites that are the final product of metabolism in a cell, tissue, organ or organism [8]. At present, numerous biochemical methods for the determination of specific metabolites in liquids or tissues of the human body are used in diagnosis. Metabolomics reveals the essence of intermediate phenotypes (changes in metabolite levels) in relation to genomic and proteomic data, the influence of the environment. Metabolites are considered not only as the main indicators for establishing the final diagnosis of certain diseases, but also as a basis for studying the pathophysiological processes of various human diseases. A thorough study of the amount of metabolites in the human body provides an opportunity to evaluate the metabolic phenotype of a person, also known as a metabotype. The determination of metabotype variations can be used to predict disease risk and diagnosis, understand molecular pathophysiology, interpret the understanding of environmental and lifestyle influences, develop and evaluate drug efficacy, toxicity, and adverse reactions [3].

The epidemic increase in obesity, insulin resistance and type 2 diabetes has put society at a dramatic increase in the risk of developing atherosclerotic diseases and the consequent increase in mortality worldwide [13,6,7,9,5].

The main causes of death in Kazakhstan in 2003 were cardiovascular diseases, corresponding to 57% of overall mortality. Half of these due to ischaemic heart disease and one third due to cerebrovascular diseases [12]

As indicated in numerous studies, the relationship between the development of cardiovascular diseases and the metabolic syndrome is characterized by obesity and an increase in visceral fat, arterial hypertension, insulin resistance (a decrease in the sensitivity of tissues to insulin and hyperinsulinemia) that cause the development of violations of carbohydrate, lipid, purine metabolism. Metabolic syndrome is a big problem and significantly increases the disability and mortality of the population. In Kazakhstan, the problem of metabolic syndrome is also topical, Kazakh scientists are studying various aspects of the metabolic syndrome, a lot of different scientific papers are devoted on this issue [1,2,10,11,4]. The main idea of the study is to estimate differences among the adult population in Kazakhstan for the detection and characterization of metabolic profiles, depending on age and body weight.

Methods

Experimental design: A total of 74 plasma samples from experimental groups, including young non-obese, young obese, old non-obese and old obese were provided for metabolomics analysis. All study participants were over 18 years of age, Kazakh nationality and without chronic diseases. The study protocol, informed consent and other types of recruiting were examined at the Local Ethics Committee of the “Center for Life Sciences” (extract from Protocol No. 16 dated 11.03.2015 of the Ethical Commission meeting at the Center for Life Sciences, Nazarbayev University). Global metabolic profiles were determined from the experimental groups outlined in the table 1. The study and analysis of the complete metabolome of 74 study participants were conducted in the “Metabolon” company, USA.

Sample accessioning: For each participant of the study, blood was taken to sterile vacutainers with K3-EDTA with clot activator and gel separator. After separation of blood components into plasma, serum and cells, the composite components were stored at -80°C until processed. Each sample was accessioned into the LIMS system (Laboratory Information Management System) and was assigned a unique identifier that was associated with the original source identifier to track all sample handling, tasks, results, etc.

Sample preparation: Samples were prepared using the automated MicroLab STAR® system from Hamilton Company. Several recovery standards were used for quality control purposes. The resulting extract was divided into five fractions: two for analysis by two separate reverse phase (RP)/UPLC-MS/MS methods with positive ion mode electrospray ionization (ESI), one for analysis by RP/UPLC-MS/MS with negative ion mode ESI, one for analysis by HILIC/UPLC-MS/MS with negative ion mode ESI, and one sample was reserved for backup. Samples were placed briefly on a TurboVap® (Zymark) to remove the organic solvent. The sample extracts were stored overnight under nitrogen before preparation for analysis.

Quality control: Several types of controls were analyzed in concert with the experimental samples: use of a pool of well-characterized human plasma served as a technical replicate throughout the data set; extracted water samples served as process blanks; and a cocktail of QC standards allowed instrument performance monitoring and aided chromatographic alignment.

Ultrahigh performance liquid chromatography-Tandem mass spectroscopy (UPLC-MS/MS): All methods utilized a Waters ACQUITY ultra-performance liquid chromatography (UPLC) and a Thermo Scientific Q-Exactive high resolution/accurate mass spectrometer interfaced with a heated electrospray ionization (HESI-II) source and Orbitrap mass analyzer operated at 35,000 mass resolution. The sample extract was dried then reconstituted in solvents compatible to each of the four methods. Each reconstitution solvent contained a series of standards at fixed concentrations to ensure injection and chromatographic consistency.

Bioinformatics: The informatics system consisted of four major components, the Laboratory Information Management System (LIMS), the data extraction and peak-identification software, data processing tools for QC and compound identification, and a collection of information interpretation and visualization tools for use by data analysts. The hardware and software foundations for these informatics components were the LAN backbone, and a database server running Oracle 10.2.0.1 Enterprise Edition.

More than 3300 commercially available purified standard compounds have been acquired and registered into LIMS for analysis on all platforms for determination of their analytical characteristics. Additional mass spectral entries have been created for structurally unnamed biochemicals, which have been identified by virtue of their recurrent nature (both chromatographic and mass spectral). These compounds have the potential to be identified by future acquisition of a matching purified standard or by classical structural analysis.

The following statistical analyses were performed in this study: Welch's two-sample t-test, matched pairs t-test, one-way and two-way ANOVA, p-values, q-values, Random forest and Principal component analysis.

Results

Metabolic indices were studied in blood plasma of 74 individuals of Kazakh nationality, taking into account age and body weight. The collected samples are divided into 4 groups depending on age and obesity status (Table 1).

Table 1.

Description of experimental groups.

GROUP	GROUP NUMBER	n	GROUP DESCRIPTION
Old and Obese	1	16	age ≥ 45y, BMI ≥ 30
Old and Non-obese	2	18	age ≥ 45y, BMI < 30
Young and Obese	3	18	age < 45y, BMI ≥ 30
Young and Non-obese	4	22	age < 45y, BMI < 30

As a result of metabolomic analysis the present dataset comprises a total of 853 compounds of known identity (named biochemicals). Following log transformation and imputation of missing values, if any, with the minimum observed value for each compound, ANOVA contrasts and Welch's two-sample *t*-test were used to identify biochemicals that differed significantly between experimental groups. A summary of the numbers of biochemicals that achieved statistical significance ($p \leq 0.05$), as well as those approaching significance ($0.05 < p < 0.10$), is shown in Tables 2 and 3. Analysis by two-way ANOVA identified biochemicals exhibiting significant interaction and main effects for experimental parameters of age and obesity.

Table 2.

The number of metabolites that showed statistical significance.

ANOVA Main Effects			
Statistically Significant Biochemicals	Age	Obesity	Obesity:Age Interaction
Total Biochemicals $p \leq 0.05$	195	158	49
Total Biochemicals $0.05<p<0.10$	62	76	42

Table 3.

Statistical comparisons of study groups for 853 named metabolites (bio-compounds) that showed changes in study participants.

Statistical comparisons					
Statistically Significant Biochemicals		Total Biochemicals $p \leq 0.05$	Biochemicals (↑↓/increased decreased)	Total Biochemicals $0.05<p<0.10$	Biochemicals (↑↓/increased decreased)
ANOVA Contrasts					
Old / Young	Non-obese	94	53|41	69	42|27
	Obese	164	118|46	73	49|24
Old obese Young non-obese		244	191|53	59	41|18
Old non-obese Young obese		133	59|74	64	28|36
Obese / Non-obese	Young	121	76|45	52	31|21
	Old	102	88|14	64	48|16
Welch's Two-Sample t-Test					
Male / Female	Young non-obese	141	120|21	64	50|14
	Young obese	192	150|42	75	48|27
	Old non-obese	59	30|29	48	22|26
	Old obese	93	70|23	66	42|24

Random Forest Analysis shows an ability to segregate groups based on metabolic profile. Random Forest Analysis (RF) is an unbiased and supervised classification technique based on an ensemble of a large number of decision trees. Using the primary groupings of old, young, obese and nonobese, RF classification analysis of plasma metabolic profiles resulted in predictive accuracy of approximately 80% in differentiating either the old vs young or obese and nonobese subjects which is greater than one would expect by random chance alone (50% accuracy for two groups), indicating that differences in biochemical profiles between groups may be suitable for biomarker discovery (Figure 1,2). In addition to this, RF classification analysis of all subjects resulted in a predictive accuracy of 64% which is greater than random chance (that is, 25% accuracy), further supporting the distinction between groups as

noted earlier. Consistently found across these multiple random forest analyses was the presence of lipid-related compounds among the most important molecules contributing to group segregation. Many of these lipid-related metabolic changes are discussed below.

Fatty acid metabolism: Several medium-chain, long-chain, polyunsaturated, and branched-chain free fatty acids (FFA) were found to be significant higher within the older Kazakhstan subjects when contrasted with younger subjects. Furthermore, this was found to be most prevalent within the older obese subjects in relation to the non-obese subjects. Differences in fatty acid availability are often indicative of a change in lipid hydrolysis, fatty acid synthesis, and/or mitochondrial β-oxidation. Consistent with the elevated free fatty acids, elevated levels of carnitine-conjugated lipids including laurylcarnitine, myristoylcarnitine, palmitoylcarnitine, and palmitoleoylcarnitine among others were also observed in the older subjects in relation to younger subjects which, when combined, may be indicative of increased transport and subsequent fatty acid β-oxidation in older and obese subjects.

Indeed, higher levels of acetylcarnitine (facilitates the movement of acetyl CoA into the matrices of the mitochondria during the oxidation of fatty acids) suggests increased β-oxidation in older subjects. Furthermore, as found in the earlier dataset, there were also significantly higher levels of the ketone body 3-hydroxybutyrate (BHBA) which can be generated from excess acetyl-CoA production during mitochondrial β-oxidation in the older subjects that was also most prevalent within the obese subjects. Interestingly, there was also a large accumulation of diacylglycerols within the obese in relation to nonobese subjects, which may be a further indication of increased lipolysis within obese subjects. These changes are consistent with increased free fatty acid accumulation and altered fatty acid oxidation in older subjects as indicated earlier.

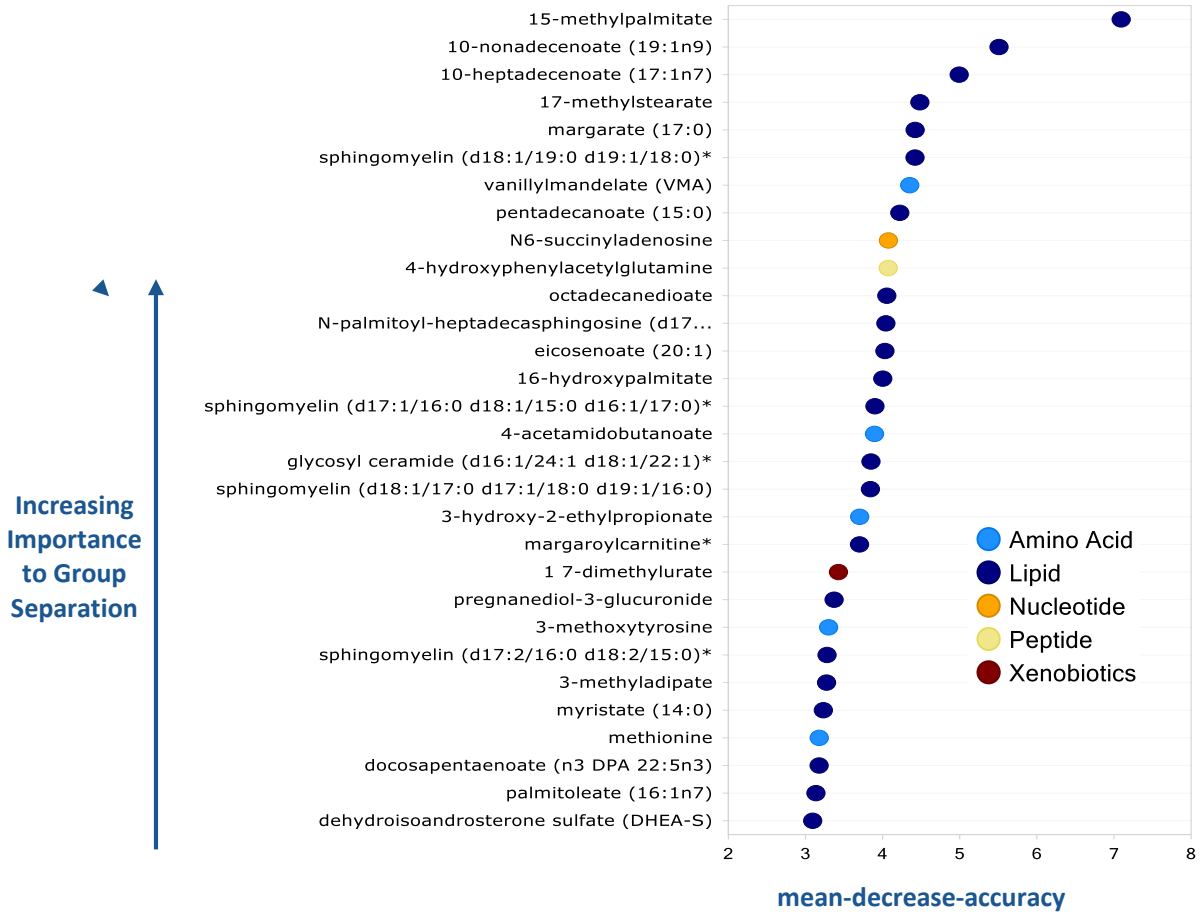

Figure 1. Random Forest classification using named metabolites in the old compared to young subjects gave a predictive accuracy of 79%.

Dicarboxylate fatty acids: While the primary route of fatty acid oxidation occurs through β-oxidation in the mitochondria and peroxisomes, ω-oxidation of fatty acids in the smooth endoplasmic reticulum can also occur, especially as a rescue pathway in genetic disorders where peroxisomal or mitochondrial fatty acid oxidation may be impaired. In the case of the older subjects, there were significant accumulations of dicarboxylic acids (DCAs) including pimelate, dodecanedioate, tetradecanedioate, hexadecanedioate and octadecanedioate, suggesting increased ω-oxidation of fatty acids in relation to younger subjects. DCAs that are produced via the ω-oxidation pathway can then be either β-oxidized in the mitochondria or peroxisomes as an energy source and the accumulation of these products may be an indication of altered or perhaps overwhelmed fatty acid β-oxidation and would be consistent with the previously noted accumulations of FFA, acylcarnitines and the ketone body BHBA in older (obese and all) subjects.

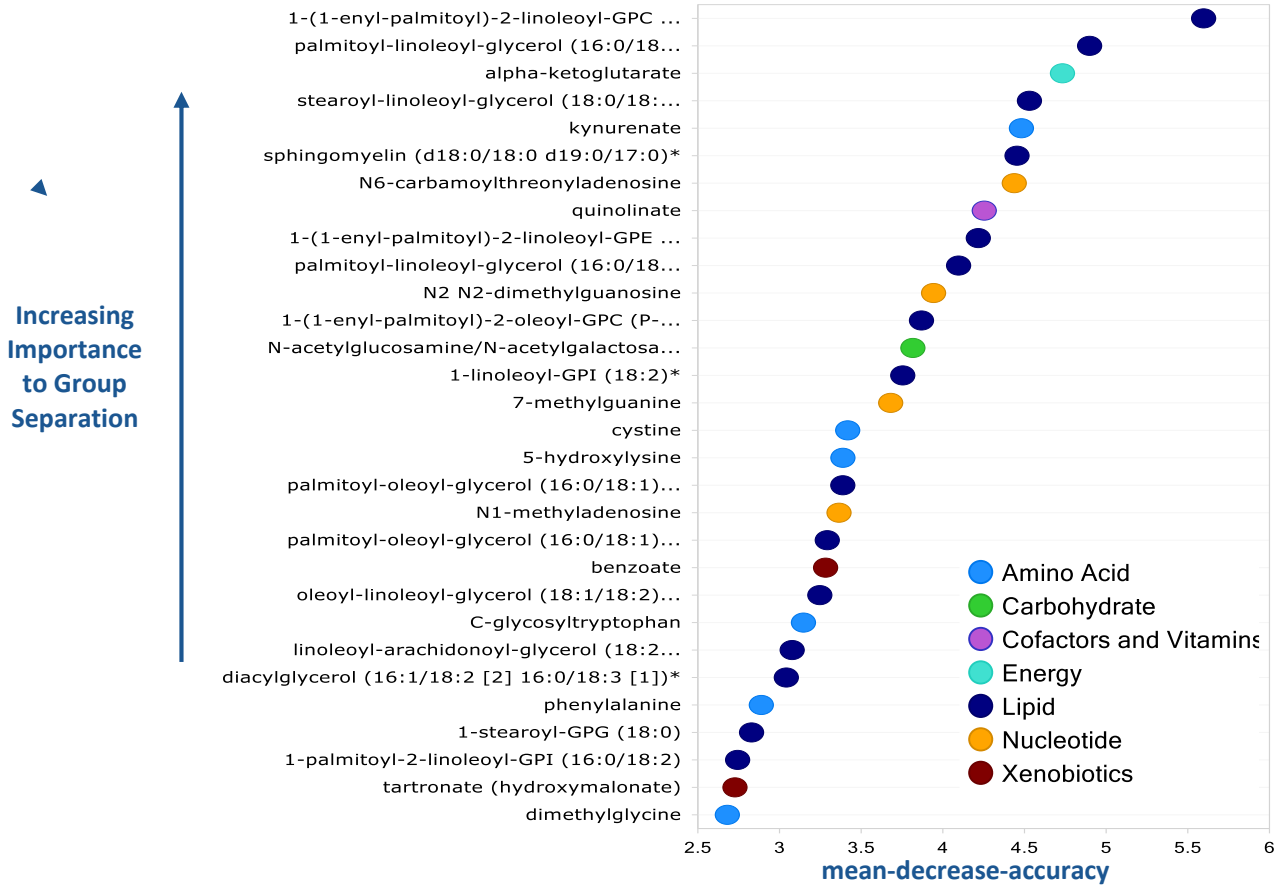

Figure 2 - Random Forest classification using named metabolites for the obese compared to nonobese subjects gave a predictive accuracy of 81%.

Monohydroxy fatty acids and other markers of oxidative stress: There were consistently higher levels of monohydroxy fatty acids with older subjects in relation to the young. Increased lipid peroxidation can be a signature of elevated oxidative stress impacting the membrane and can be a result of an imbalance between reactive oxygen species and the antioxidant systems. 2-(D)-Hydroxy fatty acids, such as 2-hydroxypalmitate and 2-hydroxystearate, are conventional lipid components and are important constituents of sphingolipids. 3-Hydroxy fatty acids such as 3-hydroxyhexanoate, 3-hydroxydecanoate, 3-hydroxysebacate and 3-hydroxylaurate are formed during ***β*** -oxidation of fatty acids in mammalian tissues with elevated concentrations in blood indicative of disorders of fatty acid oxidation. While traditional markers of

oxidative stress, including changes in glutathione (reduced or oxidized) levels, were not observed in this study, differences in additional markers of oxidative stress were present and included elevated levels of cystine (the oxidized form of cysteine) and cysteine glutathione disulfide within the obese in relation to the nonobese subjects. Additionally, xanthine which is generated from hypoxanthine through the activity of xanthine oxidase resulting in H_2O_2 formation was also found to be significantly higher within the obese in relation to the nonobese subjects and further supports a higher level of oxidative stress in the obese subjects.

Steroid levels decrease with age: There was an age-dependent decrease in steroid hormone-related metabolites including significant decreases with pregnenolone sulfate, 21-hydroxypregnenolone monosulfate, 21-hydroxypregnenolone disulfate, 17-alpha-hydroxypregnenolone 3-sulfate, 5alpha-pregnan-3beta 20-alpha-diol disulfate, 5-alpha-pregnan-3(alpha or beta) 20-beta-diol disulfate among others. Regardless of obesity status, steroid levels were consistently lower within the older subjects and are consistent with a decrease in steroidogenesis with age.

Conclusion

Metabolic indices were studied in blood plasma of 74 individuals of Kazakh nationality, taking into account age and obesity. As a result of metabolomic analysis a total of 853 compounds of known identity (named biochemicals) were identified. The vast majority were lipid-related and included markers consistent with altered fatty acid oxidation as observed in an accumulation of free fatty acids and acylcarnitines along with the ketone body BHBA and dicarboxylate fatty acids within the older obese subjects. Additional markers associated with oxidative stress, including increased monohydroxy FAs and cysteine glutathione disulfide, were also found within older as well as obese subjects. There was an age-dependent decrease in steroid hormone-related metabolites. Regardless of obesity status, steroid levels were consistently lower within the older subjects and are consistent with a decrease in steroidogenesis with age. Finally, for future studies, since there is a strong lipid signature in this study, it may be of interest to consider complex lipid panel for quantitative assessment of complex lipid-related changes in future metabolomics studies.

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References:

1. *Абылайулы Ж., Джусипов А.К., Беркинбаев С.Ф., Шалхарова Ж.С., Ошакбаев К.П., Бекжигитов С.Б., Абсеитова С.Р., Молдабек Г.К., Маймаков А.А., Ахмеджанов Н.А., Джунусбекова Г.А., Мусагалиева А.Т., Ахментаева Д.А.* Проект консенсуса по диагностике и ведению метаболического синдрома в Республике Казахстан. Разработан по результатам резолюции Республиканской научно-практической конференции «Метаболический синдром. Реалии и перспективы в кардиологии и эндокринологии» // Терапевтический вестник. 2008. №4(20). С. 27-32.

2. *Бенберин В.В., Карабаева Р.Ж.* Метаболический синдром: вопросы изучения и перспективы развития исследований // Вестник Медицинского центра Управления делами Президента Республики Казахстан. 2012. №1. С.3-5

3. *Adamski J., Suhre K.* Metabolomics platforms for genome wide association studies – linking the genome to the metabolome // Current opinion in biotechnology. 2013. V.24. P.39-47.

4. *Akanov A.A., Tulebaev K.A., Eshmanova A.K., Chaĭkovskaia V.V., Abikulova A.K., Kalmakhanov S.B., Mansharipova A.T.* Analysis of condition and prospects in geriatric care of population of Kazakhstan // Adv Gerontol. 2014. V.27 (3). P.589-95.

5. *Burke G.L., Bertoni A.G., Shea S., Tracy R., Watson K.E., Blumenthal R.S., Chung H., Carnethon M.R.* The impact of obesity on cardiovascular disease risk factors and subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis // Archives of internal medicine. 2008. V.168 (9). P.928-935.

6. *Chrostowska M., Szyndler A., Paczwa P., Narkiewicz K.* Impact of abdominal obesity on the frequency of hypertension and cardiovascular

disease in Poland - results from the IDEA study (international day for the evaluation of abdominal obesity) // Blood pressure. 2011. V.20 (3). P. 145-152.

7. *Fox K.A., Despres J.P., Richard A.J., Brette S., Deanfield J.E*. Does abdominal obesity have a similar impact on cardiovascular disease and diabetes? A study of 91,246 ambulant patients in 27 European countries // European heart journal. 2009. V.30 (24). P.3055-3063.

8. *Jordan K.W., Nordenstam J., Lauwers G.Y., Rothenberger D.A., Alavi K., Garwood M., Cheng L.L.* «Metabolomic characterization of human rectal adenocarcinoma with intact tissue magnetic resonance spectroscopy» // Diseases of the Colon & Rectum. 2009. 52 (3). P.520–5.

9. *Lavie C.J., Milani R.V., Ventura H.O.* Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss // Journal of the American College of Cardiology. 2009. V.53 (21). P.1925-1932.

10. *Oshakbayev K.P., Kenneth Alibek, Ponomarev I.O., Dukenbayeva B.A., Uderbayev N.N., Oshakbayev P., Mustafin H.* The heating value of a different location of human body lipids // Global Journal of Medical Research. 2014. Vol.13 (7). P.19-23.

11. *Oshakbayev K.P., Kenneth Alibek, Ponomarev I.O., Uderbayev N.N., Dukenbayeva B.A., Gazaliyeva M., Oshakbayev P., Kaliyeva Sh.* Body fats accumulate metabolic products: physical and chemical analysis in vitro // American Journal of Medical and Biological Research. 2014. V.2 (1). P.5-11.

12. WHO. Highlights on health in Kazakhstan. 2005. 38p.

13. *Zalesin K.C., Franklin B.A., Miller W.M., Peterson E.D., McCullough P.A.* Impact of obesity on cardiovascular disease // The Medical clinics of North America. 2011 .V.95 (5). P.919-937.

References:

1. Abylaiuly Zh., Dzhusipov A.K., Berkinbayev S.F., Shalharova Zh.S., Oshakbayev K.P., Bekzhigitov S.B., Abseitova S.R., Moldabek G.K., Maimakov A. A., Akhmetzhanov N. A., Djunusbekova G.A., Musagaliyeva A.T., Akhmentayeva D.A. Proyekt konsensusa po diagnostike i vedeniyu metabolicheskogo sindroma v Respublike Kazakhstan. Razrabotchik po rezul'tatam rezolyutsii Respublikanskoy nauchno-prakticheskoy konferentsii «Metabolicheskiy sindrom. Realii i perspektivy v kardiologii i endokrinologii» [Draft consensus on the diagnosis and management of metabolic syndrome in the Republic of Kazakhstan. Developed by the results of the resolution of the Republican Scientific and Practical Conference "Metabolic Syndrome. Realities and perspectives in cardiology and endocrinology"]. *Terapevticheskiy vestnik* [Therapeutic Herald]. 2008. 4 (20). P. 27-32. [in Russian]

2. Benberin V.V., Karabayeva R.Zh. Metabolicheskiy sindrom: voprosy izucheniya i perspektivy razvitiya issledovaniy [Metabolic syndrome: study questions and research development prospects]. *Vestnik Meditsinskogo tsentra Upravleniya delami Prezidenta Respubliki Kazakhstan* [Bulletin of the Medical Center of the Department of Affairs of the President of the Republic of Kazakhstan]. 2012. 1. P.3-5. [in Russian]

3. Adamski J., Suhre K. Metabolomics platforms for genome wide association studies – linking the genome to the metabolome. *Current opinion in biotechnology*. 2013. 24. P.39-47.

4. Akanov A.A., Tulebaev K.A., Eshmanova A.K., Chaĭkovskaia V.V., Abikulova A.K., Kalmakhanov S.B., Mansharipova A.T. Analysis of condition and prospects in geriatric care of population of Kazakhstan. *Adv Gerontol*. 2014. 27(3). P.589-595.

5. Burke G.L., Bertoni A.G., Shea S., Tracy R., Watson K.E., Blumenthal R.S., Chung H., Carnethon M.R. The impact of obesity on cardiovascular disease risk factors and subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis. *Archives of internal medicine*. 2008. 168(9). P.928-935.

6. Chrostowska M., Szyndler A., Paczwa P., Narkiewicz K. Impact of abdominal obesity on the frequency of hypertension and cardiovascular disease in Poland - results from the IDEA study (international day for the evaluation of abdominal obesity). *Blood pressure*. 2011. 20(3). P.145-152.

7. Fox K.A., Despres J.P., Richard A.J., Brette S., Deanfield J.E. Does abdominal obesity have a similar impact on cardiovascular disease and diabetes? A study of 91,246 ambulant patients in 27 European countries. *European heart journal*. 2009. 30(24). P.3055-3063.

8. Jordan K.W., Nordenstam J., Lauwers G.Y., Rothenberger D.A., Alavi K., Garwood M., Cheng L.L. Metabolomic characterization of human rectal adenocarcinoma with intact tissue magnetic resonance spectroscopy. *Diseases of the Colon & Rectum*. 2009. 52 (3). P.520–525.

9. Lavie C.J., Milani R.V., Ventura H.O. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *Journal of the American College of Cardiology.* 2009. 53(21), P.1925-1932.

10. Oshakbayev K.P., Kenneth Alibek, Ponomarev I.O., Dukenbayeva B.A., Uderbayev N.N., Oshakbayev P., Mustafin H. The heating value of a different location of human body lipids. *Global Journal of Medical Research.* 2014. 13(7). P.19-23.

11. Oshakbayev K.P., Kenneth Alibek, Ponomarev I.O., Uderbayev N.N., Dukenbayeva *B.A., Gazaliyeva M.,* Oshakbayev P., Kaliyeva Sh. Body fats accumulate metabolic products: physical and chemical analysis in vitro. *American Journal of Medical and Biological Research*. 2014. 2(1). P.5-11.

12. WHO. Highlights on health in Kazakhstan. 2005. 38p.

13. Zalesin K.C., Franklin B.A., Miller W.M., Peterson E.D., McCullough P.A. Impact of obesity on cardiovascular disease. *The Medical clinics of North America*. 2011. 95(5). P. 919-937

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