

- ACC/AHA, 2019. 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease. *Circulation*. 140: e596-646. doi:10.1161/CIR.0000000000000678
- Adeshirlarijaney, A., Gewirtz, A.T., 2020. Considering gut microbiota in treatment of type 2 diabetes mellitus. *Gut Microbes*. 11: 253–264. doi:10.1080/19490976.2020.1717719
- Agarwala, A., Liu, J., Ballantyne, C.M., Virani, S.S., 2019. The use of risk-enhancing factors to personalize ascvd risk assessment: evidence and recommendations from the 2018 aha/acc multi-society cholesterol guidelines. 13: 18. *Curr. Cardiovasc. Risk Rep.* doi:10.1007/s12170-019-0616-y
- Agarwala, A., Michos, E.D., Samad, Z., Ballantyne, C.M., Virani, S.S., 2020. The use of sex-specific factors in the assessment of women's cardiovascular risk. *Circulation* 141: 592–599. doi:10.1161/CIRCULATIONAHA.119.043429
- Agius, L., Ford, B.E., & Chachra, S.S., 2020. The metformin mechanism on gluconeogenesis and AMPK activation: The metabolite perspective. *Int. J. Mol. Sci.* 21: 3240. doi:10.3390/ijms21093240
- Ahmad, E., Sargeant, J.A., Zaccardi, F., Khunti, K., Webb, D.R., & Davies, M.J., 2020. Where does metformin stand in modern day management of type 2 diabetes? *Pharmaceuticals*. 13: 1–26. doi:10.3390/ph13120427
- Åkerborg, Ö., Spalinskas, R., Pradhananga, S., Anil, A., Höjer, P., Poujade, F.A., *et al.*, 2018. High-resolution regulatory maps connect cardiovascular risk variants to disease related pathways. *bioRxiv*. doi:10.1101/376699
- Akter, S., Goto, A., & Mizoue, T., 2017. Smoking and the risk of type 2 diabetes in Japan: A systematic review and meta-analysis. *J. Epidemiol.* 27: 553-561. doi:10.1016/j.je.2016.12.017
- Al Mansour, M.A., 2020. The prevalence and risk factors of type 2 diabetes mellitus (DMT2) in a semi-urban Saudi population. *Int. J. Environ. Res. Public Health* 17: 1–8. doi:10.3390/ijerph17010007
- Alemi, H., Khaloo, P., Mansournia, M.A., Rabizadeh, S., Salehi, S.S., Mirmiranpour, H., *et al.*, 2018. Pulse pressure and diabetes treatments. *Medicine (Baltimore)*. 97: e9791. doi:10.1097/MD.00000000000009791
- Almugadam, B.S., Liu, Y., Chen, S.M., Wang, C.H., Shao, C.Y., Ren, B.W., *et al.*, 2020. Alterations of gut microbiota in type 2 diabetes individuals and the confounding effect of antidiabetic agents. *J. Diabetes Res.* 2020. 2020: 7253978. doi:10.1155/2020/7253978
- Amankwah-Poku, M., 2019. A cross-sectional study of knowledge and awareness of type 2 diabetes mellitus in a student population in Ghana: do demographics and lifestyle make a difference. *Heal. Psychol. Behav. Med.* 7: 234–252. doi:10.1080/21642850.2019.1637261
- American Diabetes Association, 2020. Standards of medical care in diabetes. *J. Clin. Appl. Res. Educ.* 43: 1–212.
- American Diabetes Association, 2018. Standards of medical care in diabetes—2018. *Diabetes Care* 41: 14–37.
- An, H., & He, L., 2016. Current understanding of metformin effect on the control of hyperglycemia in diabetes. *J. Endocrinol.* 228: R97–R106. doi:10.1530/JOE-15-0447
- Arnett, D.K., Blumenthal, R.S., Albert, M.A., Buroker, A.B., Goldberger, Z.D., Hahn, E.J., *et al.*, 2019. 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease: a report of the american college of cardiology/american heart association task force on clinical practice guidelines. *Circulation*. 140: 596-646.

- Asgharzadeh, M., Pourasghary, S., Pourasghary, B., Nourazarian, M., & Kafil, H.S., 2016. Effective factors in controlling diabetes progression among patients in the northwest of Iran. *J. Nat. Sci. Biol. Med.* 7: 68–71. doi:10.4103/0976-9668.175075
- Asiimwe, D., Mauti, G.O., & Kiconco, R., 2020. Prevalence and risk factors associated with type 2 diabetes in elderly patients aged 45-80 years at Kanungu District. *J. Diabetes Res.* 2020. doi:10.1155/2020/5152146
- Baek, J.H., Kim, H., Kim, K.Y., & Jung, J., 2018. Insulin resistance and the risk of diabetes and dysglycemia in Korean general adult population. *Diabetes Metab. J.* 42: 296–307. doi:10.4093/dmj.2017.0106
- Bai, B., and Chen, H., 2021. Metformin: A novel weapon against inflammation. *Front. Pharmacol.* 12: 622262. doi:10.3389/fphar.2021.622262
- Bankura, B., Das, M., Kumar, P.A., Adhikary, B., Bhattacharjee, R., Goswami, S., *et al.*, 2016. Inter-patient variability in clinical efficacy of metformin in type 2 diabetes mellitus patients in West Bengal, India. *J Metab. Syndr.* 5: 198-202. doi:10.4172/2167-0943.1000198
- Bashier, A., Bin Hussain, A., Abdelgadir, E., Alawadi, F., Sabbour, H., & Chilton, R., 2019. Consensus recommendations for management of patients with type 2 diabetes mellitus and cardiovascular diseases. *Diabetol. Metab. Syndr.* 11: 80. doi:10.1186/s13098-019-0476-0
- Batchuluun, B., Sonoda, N., Takayanagi, R., & Inoguchi, T., 2014. The cardiovascular effects of metformin: conventional and new insights antidiabetic drug- metformin. *J Endocrinol Diabetes Obes* 2: 1–5.
- Bertoluci, M.C., & Rocha, V.Z., 2017. Cardiovascular risk assessment in patients with diabetes. *Diabetol. Metab. Syndr.* 9: 25. doi:10.1186/s13098-017-0225-1
- Bidmon, S., & Terlutter, R., 2015. Gender differences in searching for health information on the internet and the virtual patient-physician relationship in Germany: Exploratory results on how men and women differ and why. *J. Med. Internet Res.* 17: e156. doi:10.2196/jmir.4127
- Bloomgarden, Z., 2017. Is insulin the preferred treatment for HbA1c >9%?. *J. Diabetes* 9: 814–816. doi:10.1111/1753-0407.12575
- Boden, G., 2008. Obesity and Free Fatty Acids (FFA). *Endocrinol Metab Clin North Am.* 37: 635–665. doi:10.1016/j.ecl.2008.06.007
- Bonnet, A., Grosso, A.R., & De Almeida, F., 2017. Introns protect eukaryotic genomes from transcription-associated genetic instability. *Mol. Cell* 67: 608–621.e6. doi:10.1016/j.molcel.2017.07.002
- Borg, M.J., Jones, K.L., Sun, Z., Horowitz, M., Rayner, C.K., & Wu, T., 2019. Metformin attenuates the postprandial fall in blood pressure in type 2 diabetes. *Diabetes, Obes. Metab.* 21: 1251–1254. doi:10.1111/dom.13632
- Borgharkar, S.S., & Das, S.S., 2019. Real-world evidence of glycemic control among patients with type 2 diabetes mellitus in India: The TIGHT study. *BMJ Open Diabetes Res. Care.* 7: 654. doi:10.1136/bmjdr-2019-000654
- Boussageon, R., Supper, I., Bejan-Angoulvant, T., Kellou, N., Cucherat, M., Boissel, J.P., *et al.*, 2012. Reappraisal of metformin efficacy in the treatment of type 2 diabetes: A meta-analysis of randomised controlled trials. *PLoS Med.* 9. doi:10.1371/journal.pmed.1001204
- Bress, A.P., Colantonio, L.D., Booth, J.N., Spruill, T.M., Ravenell, J., Butler, M., *et al.*, 2017. Modifiable risk factors versus age on developing high predicted cardiovascular disease risk in blacks. *J. Am. Heart Assoc.* 6: e005054. doi:10.1161/JAHA.116.005054
- Bromage, D.I., & Yellon, D.M., 2015. The pleiotropic effects of metformin: time for

- prospective studies. *Cardiovasc. Diabetol.* 14: 109. doi:10.1186/s12933-015-0273-5
- Brown, J.B., Conner, C., & Nichols, G.A., 2010. Secondary failure of metformin monotherapy in clinical practice. *Diabetes Care.* 33: 501–506. doi:10.2337/dc09-1749
- Bukht, M.S., Ahmed, K.R., Hossain, S., Masud, P., Sultana, S., & Khanam, R., 2019. Association between physical activity and diabetic complications among Bangladeshi type 2 diabetic patients. *Diabetes Metab. Syndr. Clin. Res. Rev.* 13: 806–809. doi:10.1016/j.dsx.2018.11.069
- Cai, X., Hu, D., Pan, C., Li, G., Lu, J., Ji, Q., *et al.*, 2019. The risk factors of glycemic control, blood pressure control, lipid control in Chinese patients with newly diagnosed type 2 diabetes _ A nationwide prospective cohort study. *Sci. Rep.* 9: 1–14. doi:10.1038/s41598-019-44169-4
- Carling, D., 2017. AMPK signalling in health and disease. *Curr. Opin. Cell Biol.* 45: 31–37. doi:10.1016/j.ceb.2017.01.005
- Carrillo-Larco, R.M., Jaime Miranda, J., Gilman, R.H., Checkley, W., Smeeth, L., & Bernabe-Ortiz, A., 2018. The HOMA-IR performance to identify new diabetes cases by degree of urbanization and altitude in Peru: The CRONICAS cohort study. *J. Diabetes Res.* 2018: 7434918. doi:10.1155/2018/7434918
- Cavero-Redondo, I., Deeks, J.J., Alvarez-Bueno, C., Jolly, K., Saz-Lara, A., Price, M., *et al.*, 2021. Comparative effect of physical exercise versus statins on improving arterial stiffness in patients with high cardiometabolic risk: A network meta-analysis. *PLoS Med.* 18: e1003543. doi:10.1371/JOURNAL.PMED.1003543
- Chavez, J.A., Roach, W.G., Keller, S.R., Lane, W.S., & Lienhard, G.E., 2008. Inhibition of GLUT4 translocation by Tbc1d1, a Rab GTPase-activating protein abundant in skeletal muscle, is partially relieved by AMP-activated protein kinase activation. *J. Biol. Chem.* 283: 9187–9195. doi:10.1074/jbc.M708934200
- Chen, C., Cohrs, C.M., Stertmann, J., Bozsak, R., & Speier, S., 2017. Human beta cell mass and function in diabetes: Recent advances in knowledge and technologies to understand disease pathogenesis. *Mol. Metab.* 6: 943–957. doi:10.1016/j.molmet.2017.06.019
- Chen, C., Kassan, A., Castañeda, D., Gabani, M., Choi, S.K., & Kassan, M., 2019. Metformin prevents vascular damage in hypertension through the AMPK/ER stress pathway. *Hypertens. Res.* 42: 960–969. doi:10.1038/s41440-019-0212-z
- Chen, Y., Li, S., Brown, C., Cheatham, S., Castro, R.A., Leabman, M.K., *et al.*, 2009. Effect of genetic variation in the organic cation transporter 2 on the renal elimination of metformin. *Pharmacogenet. Genomics.* 19: 497–504. doi:10.1097/FPC.0b013e32832cc7e9
- Cheng, Y.H., Tsao, Y.C., Tzeng, I.S., Chuang, H.H., Li, W.C., Tung, T.H., *et al.*, 2017. Body mass index and waist circumference are better predictors of insulin resistance than total body fat percentage in middle-aged and elderly Taiwanese. *Medicine.* 96: e8126. doi:10.1097/MD.00000000000008126
- Cho, K., Chung, J.Y., Cho, S.K., Shin, H.W., Jang, I.J., Park, J.W., *et al.*, 2015. Antihyperglycemic mechanism of metformin occurs via the AMPK/LXR α /POMC pathway. *Sci. Rep.* 5:e8145. doi:10.1038/srep08145
- Chong, S., Ding, D., Byun, R., Comino, E., Bauman, A., & Jalaludin, B., 2017. Lifestyle changes after a diagnosis of type 2 diabetes. *Diabetes Spectr.* 30: 43–50. doi:10.2337/ds15-0044
- Chorev, M., & Carmel, L., 2012. The function of introns. *Front. Genet.* 3: 55. doi:10.3389/fgene.2012.00055
- Christensen, M.M.H., Brasch-Andersen, C., Green, H., Nielsen, F., Damkier, P., Beck-Nielsen, H., *et al.*, 2011. The pharmacogenetics of metformin and its impact on plasma metformin steady-state levels and glycosylated hemoglobin A1c. *Pharmacogenet.*

- Cosentino, F., Grant, P.J., Aboyans, V., Bailey, C.J., Ceriello, A., Delgado, V., *et al.*, 2020. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur. Heart J.* 41: 255–323. doi:10.1093/eurheartj/ehz486
- Dal Canto, E., Ceriello, A., Rydén, L., Ferrini, M., Hansen, T.B., Schnell, O., *et al.*, 2019. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications. *Eur. J. Prev. Cardiol.* 26: 25–32. doi:10.1177/2047487319878371
- Day, E.A., Ford, R.J., & Steinberg, G.R., 2017. AMPK as a therapeutic target for treating metabolic diseases. *Trends Endocrinol. Metab.* 28: 545–560. doi:10.1016/j.tem.2017.05.004
- De Cosmo, S., Viazzi, F., Pacilli, A., Giorda, C., Ceriello, A., Gentile, S., Russo, *et al.*, 2016. Predictors of chronic kidney disease in type 2 diabetes: A longitudinal study from the AMD Annals initiative. *Medicine*. 95: e4007. doi:10.1097/MD.0000000000004007
- de Jager, J., Kooy, A., Schalkwijk, C., van der Kolk, J., Lehert, P., Bets, D., Wulffelé, M.G., *et al.*, 2014. Long-term effects of metformin on endothelial function in type 2 diabetes: a randomized controlled trial. *J. Intern. Med.* 275: 59–70. doi:10.1111/joim.12128
- DeFronzo, R.A., Stonehouse, A.H., Han, J., & Wintle, M.E., 2010. Relationship of baseline HbA1c and efficacy of current glucose-lowering therapies: A meta-analysis of randomized clinical trials. *Diabet. Med.* 27: 309–317. doi:10.1111/j.1464-5491.2010.02941.x
- Dinas Kesehatan Daerah Istimewa Yogyakarta, 2019. Gambaran 10 besar penyakit pada puskesmas di Daerah Istimewa Yogyakarta sampai dengan bulan Oktober 2019. <https://www.dinkes.jogjaprov.go.id/berita/detail/gambaran-10-besar-penyakit-pada-puskesmas-di-daerah-istimewa-yogyakarta-sampai-dengan-bulan-oktober-2019> (accessed 3.31.21).
- Dinas Kesehatan Kabupaten Sleman, 2020. Profil kesehatan Kabupaten Sleman tahun 2020, Dinas Kesehatan Sleman.
- Dobrică, E.C., Găman, M.A., Cozma, M.A., Bratu, O.G., Stoian, A.P., & Diaconu, C.C., 2019. Polypharmacy in type 2 diabetes mellitus: Insights from an internal medicine department. *Medicina*. 55: 436. doi:10.3390/medicina55080436
- Duan, Q., Song, P., Ding, Y., & Zou, M.H., 2017. Activation of AMP-activated protein kinase by metformin ablates angiotensin II-induced endoplasmic reticulum stress and hypertension in mice in vivo. *Br. J. Pharmacol.* 174: 2140–2151. doi:10.1111/bph.13833
- Duckworth, W., Abraira, C., Moritz, T., Reda, D., Emanuele, N., Reaven, P.D., *et al.*, 2009. Glucose control and vascular complications in veterans with type 2 diabetes. *N. Engl. J. Med.* 360: 129–139. doi:10.1056/NEJMoa0808431
- Dujic, T., Zhou, K., Donnelly, L.A., Tavendale, R., Palmer, C.N.A., & Pearson, E.R., 2015. Association of organic cation transporter 1 with intolerance to metformin in type 2 diabetes: A GoDARTS study. *Diabetes*. 64: 1786–1793. doi:10.2337/db14-1388
- Dujic, T., Zhou, K., Yee, S., van Leeuwen, N., de Keyser, C., Javorský, M., *et al.*, 2017. Variants in pharmacokinetic transporters and glycemic response to metformin: A Metgen Meta-Analysis. *Clin. Pharmacol. Ther.* 101: 763–772. doi:10.1002/cpt.567
- Duque, A.L.R.F., Monteiro, M., Adorno, M.A.T., Sakamoto, I.K., Sivieri, K., 2016. An exploratory study on the influence of orange juice on gut microbiota using a dynamic colonic model. *Food Res. Int.* 84: 160–169. doi:10.1016/j.foodres.2016.03.028
- Dwivani, C., Harijadi, K., & Suhadi, R., 2018. Perbandingan lima metode estimasi risiko 10 tahun penyakit kardiovaskuler pada masyarakat Kabupaten Sleman- Yogyakarta. *Jurnal*

- Eckart, A., Struja, T., Kutz, A., Baumgartner, A., Baumgartner, T., Zurfluh, S., *et al.*, 2020. Relationship of nutritional status, inflammation, and serum albumin levels during acute illness: A prospective study. *Am. J. Med.* 133: 713–722.e7. doi:10.1016/j.amjmed.2019.10.031
- Einarson, T.R., Acs, A., Ludwig, C., & Panton, U.H., 2018. Prevalence of cardiovascular disease in type 2 diabetes: A systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovasc. Diabetol.* 17: 83. doi:10.1186/s12933-018-0728-6
- El-Lebedy, D., Raslan, H.M., & Mohammed, A.M., 2016. Apolipoprotein E gene polymorphism and risk of type 2 diabetes and cardiovascular disease. *Cardiovasc. Diabetol.* 15: 1–11. doi:10.1186/s12933-016-0329-1
- ElKafrawi, N., Shoaib, A., & Abd Elaal Elghanam, M., 2017. Measurement of waist circumference as a screening tool for type 2 diabetes mellitus in female patients. *Menoufia Med. J.* 30: 168. doi:10.4103/1110-2098.211528
- Ellis, K.L., Palmer, B.R., Frampton, C.M., Troughton, R.W., Doughty, R.N., Whalley, G.A., *et al.*, 2013. Genetic variation in the renin-angiotensin-aldosterone system is associated with cardiovascular risk factors and early mortality in established coronary heart disease. *J. Hum. Hypertens.* 27: 237–244. doi:10.1038/jhh.2012.24
- Ellulu, M.S., Patimah, I., Khaza'ai, H., Rahmat, A., & Abed, Y., 2017. Obesity & inflammation: The linking mechanism & the complications. *Arch. Med. Sci.* 13: 851–863. doi:10.5114/aoms.2016.58928
- Esteves, J.V., Enguita, F.J., & Machado, U.F., 2017. MicroRNAs-mediated regulation of skeletal muscle GLUT4 expression and translocation in insulin resistance. *J. Diabetes Res.* 2017: 7267910. doi:10.1155/2017/7267910
- Ewart, M.-A., & Kennedy, S., 2012. Diabetic cardiovascular disease – AMP-activated protein kinase (AMPK) as a therapeutic target. *Cardiovasc. Hematol. Agents Med. Chem.* 10: 190–211. doi:10.2174/187152512802651015
- Fajarini, I.A., & Sartika, R.A.D., 2019. Obesity as type 2 diabetes common comorbidity: study of type 2 diabetes patients' eating behaviour and other determinants in Jakarta, Indonesia. *Kesmas J. Kesehat. Masy. Nas. (National Public Heal. Journal)* 13: 157–163. doi:10.21109/kesmas.v13i4.2483
- Feinman, R.D., Pogozelski, W.K., Astrup, A., Bernstein, R.K., Fine, E.J., Westman, E.C., *et al.*, 2015. Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base. *Nutrition.* 31: 1-13. doi:10.1016/j.nut.2014.06.011
- Fernandes, G., Sawhney, B., Hannachi, H., Liu, J., Wang, T., Fu, A.Z., *et al.*, 2020. Distance to glycemic goal at the time of treatment intensification in patients with type 2 diabetes mellitus failing metformin monotherapy in the United States. *Curr. Med. Res. Opin.* 36: 741–748. doi:10.1080/03007995.2020.1722623
- Fernández-Real, J.M., Pickup, J.C., 2008. Innate immunity, insulin resistance and type 2 diabetes. *Trends Endocrinol. Metab.* 19: 10–16. doi:10.1016/j.tem.2007.10.004
- Ferrannini, E., Iozzo, P., Virtanen, K.A., Honka, M.-J., Bucci, M., & Nuutila, P., 2018. Adipose tissue and skeletal muscle insulin-mediated glucose uptake in insulin resistance: role of blood flow and diabetes. *Am. J. Clin. Nutr.* 108: 749–758. doi:10.1093/ajcn/nqy162
- Florez, J.C., 2017. The pharmacogenetics of metformin. *Diabetologia.* 60: 1648–1655. doi:10.1007/s00125-017-4335-y
- Flynn, C., & Bakris, G.L., 2013. Noninsulin glucose-lowering agents for the treatment of patients on dialysis. *Nat. Rev. Nephrol.* 9: 147–153. doi:10.1038/nrneph.2013.12

- Foretz, M., Hébrard, S., Leclerc, J., Zarrinpashneh, E., Soty, M., Mithieux, G., *et al.*, 2010. Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway via a decrease in hepatic energy state. *J. Clin. Invest.* 120: 2355-2369. doi:10.1172/JCI40671
- Franks, P.W., & Shungin, D., 2011. The interplay of lifestyle and genetic susceptibility in Type 2 diabetes risk review. *Diabetes Manag.* 1: 299–307. doi:10.2217/DMT.11.3
- Fullerton, M.D., Galic, S., Marcinko, K., Sikkema, S., Pulinilkunnil, T., Chen, Z.-P., *et al.*, 2013. Single phosphorylation sites in Acc1 and Acc2 regulate lipid homeostasis and the insulin-sensitizing effects of metformin. *Nat Med.* 19: 1649–1654. doi:10.1038/nm.3372
- Gangopadhyay, K., & Singh, P., 2017. Consensus statement on dose modifications of antidiabetic agents in patients with hepatic impairment. *Indian J. Endocrinol. Metab.* 21: 341. doi:10.4103/ijem.IJEM_512_16
- Gao, Z., Chen, Z., Sun, A., Deng, X., 2019. Gender differences in cardiovascular disease. *Med. Nov. Technol. Devices.* 4: 100025. doi:10.1016/j.medntd.2019.100025
- Garber, A.J., Abrahamson, M.J., Barzilay, J.I., Blonde, L., Bloomgarden, Z.T., Bush, M.A., *et al.*, 2018. Consensus statement by the American Association of Clinical Endocrinologist and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2018 executive summary. *Endocr. Pract.* 24: 91–120. doi:10.4158/CS-2017-0153
- Garcia, D., & Shaw, R.J., 2017. AMPK: mechanisms of cellular energy sensing and restoration of metabolic balance Daniel. *Mol Cell.* 66: 789–800.
- García-Rubi, E., & Calles-Escandón, J., 2017. Insulin resistance and type 2 diabetes mellitus. *Arch. Med. Res.* 30: 459–464. doi:10.1016/S0188-4409(99)00077-6
- Garimella, S., Seshayamma, V., Rao, H.J., Kumar, S., Kumar, U., & Saheb, S.H., 2016. Effect of metformin on lipid profile of type II diabetes quick response code. *Orig. Res. Artic. Int. J. Integr. Med. Sci.* 3: 449–53. doi:10.16965/ijims.2016.155
- Gaudet, M.M., Milne, R.L., Cox, A., Camp, N.J., Goode, E.L., Humphreys, M.K., *et al.*, 2009. Five polymorphisms and breast cancer risk: Results from the breast cancer association consortium. *Cancer Epidemiol. Biomarkers Prev.* 18: 1610–1616. doi:10.1158/1055-9965.EPI-08-0745
- Gerstein, H., Miller, M.E., Byington, R.P., Goff, D.C., Bigger, J.T., Buse, J.B., *et al.*, 2008. Effects of intensive glucose lowering in type 2 diabetes. *N. Engl. J. Med.* 358: 2545–2559. doi:10.1056/NEJMoa0802743
- Giannarelli, R., Aragona, M., Coppelli, A., & Prato, S. Del, 2008. Diabetes & Metabolism., /data/revues/12623636/00294-C2/6S28/. Elsevier Masson.
- Golden, T.N., Simmons, R.A., 2021. Immune dysfunction in developmental programming of type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* 17: 235-245. doi:10.1038/s41574-020-00464-z
- Goliasch, G., Silbernagel, G., Kleber, M.E., Grammer, T.B., Pilz, S., Tomaschitz, A., *et al.*, 2017. Refining Long-Term Prediction of Cardiovascular Risk in Diabetes - The VILDIA Score. *Sci. Rep.* 7: 1–9. doi:10.1038/s41598-017-04935-8
- Gopoju, R., Panangipalli, S., & Kotamraju, S., 2018. Metformin treatment prevents SREBP2-mediated cholesterol uptake and improves lipid homeostasis during oxidative stress-induced atherosclerosis. *Free Radic. Biol. Med.* 118: 85–97. doi:10.1016/j.freeradbiomed.2018.02.031
- Gowans, G.J., Hawley, S.A., Ross, F.A., & Hardie, D.G., 2013. AMP is a true physiological regulator of amp-activated protein kinase by both allosteric activation and enhancing net phosphorylation. *Cell Metab.* 18: 556–566. doi:10.1016/j.cmet.2013.08.019
- Graham, G.G., Punt, J., Arora, M., Day, R.O., Doogue, M.P., Duong, J.K., *et al.*, 2011. Clinical pharmacokinetics of metformin. *Clin. Pharmacokinet.* 50: 81–98.

- Griffin, S.J., Leaver, J.K., & Irving, G.J., 2017. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. *Diabetologia*. 60: 1620–1629. doi:10.1007/s00125-017-4337-9
- Grimm, G., Haslacher, H., Kampitsch, T., Endler, G., Marsik, C., Schickbauer, T., *et al.*, 2009. Sex differences in the association between albumin and all-cause and vascular mortality. *Eur. J. Clin. Invest.* 39: 860–865. doi:10.1111/j.1365-2362.2009.02189.x
- Gurung, M., Li, Z., You, H., Rodrigues, R., Jump, D.B., Morgun, A., *et al.*, 2020. Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine*. 51: 102590. doi:10.1016/j.ebiom.2019.11.051
- Haas, A. V., & McDonnell, M.E., 2018. Pathogenesis of Cardiovascular Disease in Diabetes. *Endocrinol. Metab. Clin. North Am.* 47: 51–63. doi:10.1016/j.ecl.2017.10.010
- Habegger, K.M., Hoffman, N.J., Ridenour, C.M., Brozinick, J.T., & Elmendorf, J.S., 2012. AMPK enhances insulin-stimulated GLUT4 regulation via lowering membrane cholesterol. *Endocrinology* 153: 2130–41. doi:10.1210/en.2011-2099
- Han, S.J., Kim, H.J., Kim, D.J., Lee, K.W., & Cho, N.H., 2017. Incidence and predictors of type 2 diabetes among Koreans: A 12-year follow up of the Korean Genome and Epidemiology Study. *Diabetes Res. Clin. Pract.* 123: 173–180. doi:10.1016/j.diabres.2016.10.004
- Harbuwono, D.S., Tahapary, D.L., Tarigan, T.J.E., & Yunir, E., 2020. New proposed cut-off of waist circumference for central obesity as risk factor for diabetes mellitus: Evidence from the Indonesian Basic National Health Survey. *PLoS One*. 15: e0242417. doi:10.1371/journal.pone.0242417
- Hardie, D.G., Ross, F.A., & Hawley, S.A., 2017. Europe PMC Funders Group AMPK - a nutrient and energy sensor that maintains energy homeostasis. *Nat Rev Mol Cell Biol.* 13: 251–262. doi:10.1038/nrm3311.AMPK
- Hastuti, J., Kagawa, M., Byrne, N.M., & Hills, A.P., 2017. Determination of new anthropometric cut-off values for obesity screening in Indonesian adults. *Asia Pac. J. Clin. Nutr.* 26: 650–656. doi:10.6133/apjcn.072016.09
- Hawley, S.A., Pan, D.A., Mustard, K.J., Ross, L., Bain, J., Edelman, A.M., *F et al.*, 2005. Calmodulin-dependent protein kinase kinase- β is an alternative upstream kinase for AMP-activated protein kinase. *Cell Metab.* 2: 9–19. doi:10.1016/j.cmet.2005.05.009
- He, L., & Wondisford, F.E., 2015. Metformin action: concentrations matter. *Cell Metab.* 21: 159–162. doi:10.1016/j.cmet.2015.01.003
- Hegab, Z., Gibbons, S., Neyses, L., & Mamas, M.A., 2012. Role of advanced glycation end products in cardiovascular disease. *World J. Cardiol.* 4: 90–102. doi:10.4330/wjc.v4.i4.90
- Hempe, J.M., Liu, S., Myers, L., Mccarter, R.J., Buse, J.B., Fonseca, V., 2015. The hemoglobin glycation index identifies subpopulations with harms or benefits from intensive treatment in the ACCORD trial. *Diabetes Care* 38: 1067–1074. doi:10.2337/dc14-1844
- Herman, W.H., Pan, Q., Edelstein, S.L., Mather, K.J., Perreault, L., Barrett-Connor, E., *et al.*, 2017. Impact of lifestyle and metformin interventions on the risk of progression to diabetes and regression to normal glucose regulation in overweight or obese people with impaired glucose regulation. *Diabetes Care*. 40: 1668–1677. doi:10.2337/dc17-1116
- Hieronymus, L., Griffin, S., 2015. Role of amylin in type 1 and type 2 diabetes. *Diabetes Educ.* 41: 47S–56S. doi:10.1177/0145721715607642
- Hirst, J.A., Farmer, A.J., Ali, R., Roberts, N.W., & Stevens, R.J., 2012. Quantifying the effect of metformin treatment and dose on glycemic control. *Diabetes Care*. 35. doi:10.2337/dc11-1465

- Horáková, D., Štěpánek, L., Janout, V., Janoutová, J., Pastucha, D., Kollárová, H., *et al.*, 2019. Optimal homeostasis model assessment of insulin resistance (HOMA-IR) cut-offs: A cross-sectional study in the Czech population. *Med.* 55: 158. doi:10.3390/medicina55050158
- Horikoshi, M., Hara, K., Ohashi, J., Miyake, K., Tokunaga, K., Ito, C., *et al.*, 2006. A polymorphism in the AMPK α 2 subunit gene is in the Japanese population. *Diabetes.* 55: 919–923.
- Hu, Y., Zheng, S., Zhao, J., Tan, I., Butlin, M., Avolio, A., *et al.*, 2020. Relationship between obesity phenotypes and cardiovascular risk in a Chinese cohort. *Artery Res.* 26: 34–41. doi:10.2991/artres.k.200306.001
- Huebschmann, A.G., Huxley, R.R., Kohrt, W.M., Zeitler, P., Regensteiner, J.G., & Reusch, J.E.B., 2019. Sex differences in the burden of type 2 diabetes and cardiovascular risk across the life course. *Diabetologia.* 62: 1761–1772. doi:10.1007/s00125-019-4939-5
- International Diabetes Foundation, 2018. IDF South East Asia. *Int. Diabetes Found.* <https://idf.org/our-network/regions-members/south-east-asia/welcome.html> (accessed 2.11.19).
- Islam, S.M.S., Alam, D.S., Wahiduzzaman, M., Niessen, L.W., Froeschl, G., Ferrari, U., *et al.*, 2015. Clinical characteristics and complications of patients with type 2 diabetes attending an urban hospital in Bangladesh. *Diabetes Metab. Syndr. Clin. Res. Rev.* 9: 7–13. doi:10.1016/J.DSX.2014.09.014
- Isoda, K., Young, J.L., Zirlik, A., MacFarlane, L.A., Tsuboi, N., Gerdes, N., *et al.*, 2006. Metformin inhibits proinflammatory responses and nuclear factor- κ B in human vascular wall cells. *Arterioscler. Thromb. Vasc. Biol.* 26: 611–617. doi:10.1161/01.ATV.0000201938.78044.75
- Jablonski, K.A., McAteer, J.B., De Bakker, P.I.W., Franks, P.W., Pollin, T.I., Hanson, R.L., *et al.*, 2010. Common variants in 40 genes assessed for diabetes incidence and response to metformin and lifestyle intervention in the diabetes prevention program. *Diabetes.* 59: 2672–2681. doi:10.2337/db10-0543
- Janić, M., Volčanšek, Š., Lunder, M., & Janež, A., 2017. Metformin : from mechanisms of action to advanced clinical use. *Zdr. Vestn.* 86: 138–157.
- Jia, G., DeMarco, V.G., & Sowers, J.R., 2016. Insulin resistance and hyperinsulinaemia in diabetic cardiomyopathy. *Nat. Rev. Endocrinol.* 12: 144–153. doi:10.1038/nrendo.2015.216
- Jiang, M., Li, R., & Zhang, S., 2014. Investigation of AMPK α 2 subunit gene polymorphism of type 2 diabetes mellitus in Han populations in Chongqing | JIANG | Medical Journal of Chinese People's Liberation Army. *PLAMJ.* 39. doi:10.11855/j.issn.0577-7402.2014.09.11
- Jiang, Y., Huang, W., Wang, J., Xu, Z., He, J., Lin, X., *et al.*, 2014. Metformin plays a dual role in min6 pancreatic β cell function through AMPK-dependent autophagy. *Int. J. Biol. Sci.* 10: 268–277. doi:10.7150/ijbs.7929
- Jiang, Z., Sun, T. yu, He, Y., Gou, W., Zuo, L. shi yuan, Fu, Y., *et al.*, 2020. Dietary fruit and vegetable intake, gut microbiota, and type 2 diabetes: results from two large human cohort studies. *BMC Med.* 18: 371. doi:10.1186/s12916-020-01842-0
- Jo, B.-S., & Choi, S.S., 2015. Introns: the functional benefits of introns in genomes. *Genomics Inform.* 13: 112–8. doi:10.5808/GI.2015.13.4.112
- Jung, R., Lübcke, C., Wagener, C., & Neumaier, M., 1997. Reversal of RT-PCR inhibition observed in heparinized clinical specimens. *Biotechniques.* 23: 24–28. doi:10.2144/97231bm03
- Kahn, S., & Cooper, M., Del Prato, S., 2015. Pathophysiology and treatment of type 2 diabetes: perspective on the past, present and future. *Lancet.* 383: 1068–1083.

doi:10.1016/S0140-6736(13)62154-6

- Kanto, K., Ito, H., Noso, S., Babaya, N., Hiromine, Y., Taketomo, Y., *et al.*, 2018. Effects of dosage and dosing frequency on the efficacy and safety of high-dose metformin in Japanese patients with type 2 diabetes mellitus. *J. Diabetes Investig.* 9: 587–593. doi:10.1111/jdi.12755
- Kashi, Z., Mahrooz, A., Kianmehr, A., & Alizadeh, A., 2016. The role of metformin response in lipid metabolism in patients with recent-onset type 2 diabetes: HbA1c level as a criterion for designating patients as responders or nonresponders to metformin. *PLoS One*. 11: e0151543. doi:10.1371/journal.pone.0151543
- Katsuyama, H., & Yanai, H., 2019. Effects of metformin monotherapy on metabolic parameters in Japanese patients with type 2 diabetes. *J. Endocrinol. Metab.* 9: 18–21. doi:10.14740/jem549
- Kautzky-Willer, A., Harreiter, J., & Pacini, G., 2016. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. *Endocr. Rev.* 37: 278–316. doi:10.1210/er.2015-1137
- KDIGO, 2013. Chapter 1: definition and classification of CKD. *Kidney Int. Suppl.* 3: 19–62. doi:10.1038/kisup.2012.64
- Keller, U., 2019. Nutritional laboratory markers in malnutrition. *J. Clin. Med.* 8: 775. doi:10.3390/jcm8060775
- Kemenkes RI, 2020. Profil kesehatan Indonesia tahun 2019, Kementerian Kesehatan Republik Indonesia.
- Kementerian Kesehatan RI, 2014. Situasi dan analisis diabetes. *Pus. Data dan Inf.* <http://www.depkes.go.id/resources/download/pusdatin/infodatin/infodatin-diabetes.pdf> (accessed 2.11.19).
- Keshavarz, P., Inoue, H., Nakamura, N., Yoshikawa, T., Tanahashi, T., & Itakura, M., 2008. Single nucleotide polymorphisms in genes encoding LKB1 (STK11), TORC2 (CRTC2) and AMPK α 2-subunit (PRKAA2) and risk of type 2 diabetes. *Mol. Genet. Metab.* 93: 200–209. doi:10.1016/j.ymgme.2007.08.125
- Khalili, L., Alipour, B., Jafar-Abadi, M.A., Faraji, I., Hassanlilou, T., Abbasi, M.M., *et al.*, 2019. The effects of lactobacillus casei on glycemic response, serum sirtuin1 and fetuin-A levels in patients with type 2 diabetes mellitus: A randomized controlled trial. *Iran. Biomed. J.* 23: 68–77. doi:10.29252/IBJ.23.1.68
- Kido, Y., 2017. Gene–environment interaction in type 2 diabetes. *Diabetol. Int.* 8: 7–13. doi:10.1007/s13340-016-0299-2
- Kim, J., Kundu, M., Viollet, B., & Guan, K.-L., 2011. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat. Cell Biol.* 13: 132–41. doi:10.1038/ncb2152
- Kim, J., Yang, G., Kim, Y., Kim, J., & Ha, J., 2016. AMPK activators: Mechanisms of action and physiological activities. *Exp. Mol. Med.* 48: e224-12. doi:10.1038/emm.2016.16
- Kitada, M., Koya, D., 2013. SIRT1 in type 2 diabetes: Mechanisms and therapeutic potential. *Diabetes Metab. J.* 37: 315-325. doi:10.4093/dmj.2013.37.5.315
- Ko, S.H., Hur, K.Y., Rhee, S.Y., Kim, N.H., Moon, M.K., Park, S.O., *et al.*, 2017. Antihyperglycemic agent therapy for adult patients with type 2 diabetes mellitus 2017: A position statement of the Korean diabetes association. *Korean J. Intern. Med.* 32: 947–958. doi:10.3904/kjim.2017.298
- Kobashigawa, L.C., Xu, Y.C., Padbury, J.F., Tseng, Y.T., & Yano, N., 2014. Metformin protects cardiomyocyte from doxorubicin induced cytotoxicity through an AMP-activated protein kinase dependent signaling pathway: An in Vitro study. *PLoS One*. 9. doi:10.1371/journal.pone.0104888
- Kosiborod, M., Gomes, M.B., Nicolucci, A., Pocock, S., Rathmann, W., Shestakova, M. V.,

- Kote, N., & Ranganath, M.D., 2017. A comparative study of glomerular filtration rate in normal healthy controls and type 2 diabetes mellitus patients in South India. *Int. J. Clin. Exp. Physiol.* 4: 148. doi:10.4103/ijcep.ijcep
- Kristensen, J.M., Treebak, J.T., Schjerling, P., Goodyear, L., & Wojtaszewski, J.F.P., 2014. Two weeks of metformin treatment induces AMPK-dependent enhancement of insulin-stimulated glucose uptake in mouse soleus muscle. *AJP Endocrinol. Metab.* 306: E1099–E1109. doi:10.1152/ajpendo.00417.2013
- Kuan, I.H.S., Wilson, L.C., Leishman, J.C., Cosgrove, S., Walker, R.J., Putt, T.L., *et al.*, 2021. Metformin doses to ensure efficacy and safety in patients with reduced kidney function. *PLoS One.* 16: e0246247. doi:10.1371/journal.pone.0246247
- Lachance, J., 2016. Hardy-Weinberg Equilibrium and Random Mating, in: Encyclopedia of Evolutionary Biology. Elsevier Inc., pp. 208–211. doi:10.1016/B978-0-12-800049-6.00022-6
- Lahiri, D.K., & Schnabel, B., 1993. DNA isolation by a rapid method from human blood samples: Effects of MgCl₂, EDTA, storage time, and temperature on DNA yield and quality. *Biochem. Genet.* 31: 321–328. doi:10.1007/bf02401826
- Lam, N.Y.L., Rainer, T.H., Chiu, R.W.K., & Lo, Y.M.D., 2004. EDTA is a better anticoagulant than heparin or citrate for delayed blood processing for plasma DNA analysis. *Clin. Chem.* 50: 256–257. doi:10.1373/clinchem.2003.026013
- Lang, A., Kuss, O., Filla, T., & Schlesinger, S., 2020. Association between per capita sugar consumption and diabetes prevalence mediated by the body mass index: results of a global mediation analysis. *Eur. J. Nutr.* 1–9. doi:10.1007/s00394-020-02401-2
- Latifah, N. L., 2017. Hubungan durasi penyakit dan kadar gula darah dengan keluhan subyektif penderita diabetes melitus. *J. Berk. Epidemiol.* 5: 231–239. doi:10.20473/jbe.v5i2.2017.231-239
- Lechner, K., von Schacky, C., McKenzie, A.L., Worm, N., Nixdorff, U., Lechner, B., *et al.*, 2020. Lifestyle factors and high-risk atherosclerosis: Pathways and mechanisms beyond traditional risk factors. *Eur. J. Prev. Cardiol.* 27: 394–406. doi:10.1177/2047487319869400
- Lee, J.-M., Seo, W.-Y., Song, K.-H., Chanda, D., Kim, Y.D., Kim, D.-K., *et al.*, 2010. AMPK-dependent repression of hepatic gluconeogenesis via disruption of CREB.CRTC2 complex by orphan nuclear receptor small heterodimer partner. *J. Biol. Chem.* 285: 32182–91. doi:10.1074/jbc.M110.134890
- Li, Q., Li, C., Li, H., Zeng, L., Kang, Z., Mao, Y., *et al.*, 2018. Effect of AMP-activated protein kinase subunit alpha 2 (PRKAA2) genetic polymorphisms on susceptibility to type 2 diabetes mellitus and diabetic nephropathy in a Chinese population: PRKAA2. *J. Diabetes.* 10: 43–49. doi:10.1111/1753-0407.12553
- Li, Q., Li, C., Li, H., Zeng, L., Kang, Z., Mao, Y., *et al.*, 2017a. STK11 rs2075604 Polymorphism is associated with metformin efficacy in Chinese type 2 diabetes mellitus. *Int. J. Endocrinol.* 2017: 3402808. doi:10.1155/2017/3402808
- Li, Q., Li, C., Li, H., Zeng, L., Kang, Z., Mao, Y., *et al.*, 2017b. STK11 rs2075604 Polymorphism is associated with metformin efficacy in Chinese type 2 diabetes mellitus. *Int. J. Endocrinol.* 2017. doi:10.1155/2017/3402808
- Li, Y., Xu, S., Mihaylova, M., Zheng, B., Hou, X., Jiang, B., *P et al.*, 2011. AMPK phosphorylates and inhibits SREBP activity to attenuate hepatic steatosis and atherosclerosis in diet-induced insulin resistant mice. *Cell Metab.* 13: 376–388. doi:10.1016/j.cmet.2011.03.009

- Lim, L.L., Brnabic, A.J.M., Chan, S.P., Ibrahim, L., Paramasivam, S.S., Ratnasingam, J., *et al.*, 2017. Relationship of glycated hemoglobin, and fasting and postprandial hyperglycemia in type 2 diabetes mellitus patients in Malaysia. *J. Diabetes Investig.* 8: 453–461. doi:10.1111/jdi.12596
- Lim, M., & Kim, J., 2020. Association between fruit and vegetable consumption and risk of metabolic syndrome determined using the Korean Genome and Epidemiology Study (KoGES). *Eur. J. Nutr.* 59: 1667–1678. doi:10.1007/s00394-019-02021-5
- Lin, H., Hargreaves, K.A., Li, R., Reiter, J.L., Wang, Y., Mort, M., *et al.*, 2019. RegSNPs-intron: A computational framework for predicting pathogenic impact of intronic single nucleotide variants. *Genome Biol.* 20: 254. doi:10.1186/s13059-019-1847-4
- Lipska, K.J., Bailey, C.J., & Inzucchi, S.E., 2011. Use of metformin in the setting of mild-to-moderate renal insufficiency. *Diabetes Care.* 34: 1431–1437. doi:10.2337/dc10-2361
- Litwak, L., Goh, S.Y., Hussein, Z., Malek, R., Prusty, V., & Khamseh, M.E., 2013. Prevalence of diabetes complications in people with type 2 diabetes mellitus and its association with baseline characteristics in the multinational A1chieve study. *Diabetol. Metab. Syndr.* 5: 1–10. doi:10.1186/1758-5996-5-57
- Liu, Q., Li, S., Quan, H., & Li, J., 2014. Vitamin B 12 status in metformin treated patients: systematic review. *PLoS One.* 9: 1–6. doi:10.1371/journal.pone
- Liu, Y., Ye, W., Chen, Q., Zhang, Y., Kuo, C.H., Korivi, M., 2019. Resistance exercise intensity is correlated with attenuation of HbA1c and insulin in patients with type 2 diabetes: A systematic review and meta-analysis. *Int. J. Environ. Res. Public Health.* 16: 140. doi:10.3390/ijerph16010140
- Lloyd-Jones, D.M., Bennett, G., Coady, S., D, R.B., Gibbons, R., Greenland, P., Lackland, D.T., *et al.*, 2014. 2013 ACC/AHA guideline on the assessment of cardiovascular risk. *Circulation.* 129: 49–73. doi:10.1161/01.cir.0000437741.48606.98
- Lu, Q., Li, X., Liu, J., Sun, X., Rousselle, T., Ren, D., *et al.*, 2019. AMPK is associated with the beneficial effects of antidiabetic agents on cardiovascular diseases. *Biosci. Rep.* 39: BSR20181995. doi:10.1042/BSR20181995
- Luo, S., Schooling, C.M., Wong, I.C.K., & Au Yeung, S.L., 2020. Evaluating the impact of AMPK activation, a target of metformin, on risk of cardiovascular diseases and cancer in the UK Biobank: a Mendelian randomisation study. *Diabetologia.* 63: 2349–2358. doi:10.1007/s00125-020-05243-z
- Ma, J., Liu, L.Y., Wu, P.H., Liao, Y., Tao, T., & Liu, W., 2014. Comparison of metformin and repaglinide monotherapy in the treatment of new onset type 2 diabetes mellitus in China. *J. Diabetes Res.* 2014: 294017. doi:10.1155/2014/294017
- Ma, Y., Yang, F., Wang, Y., Du, Z., Liu, D., Guo, H., *et al.*, 2012. CaMKK β is involved in AMP-activated protein kinase activation by baicalin in LKB1 deficient cell lines. *PLoS One.* 7: e47900. doi:10.1371/journal.pone.0047900
- Maddatu, J., Anderson-Baucum, E., & Evans-Molina, C., 2017. Smoking and the risk of type 2 diabetes. *Transl. Res.* 184: 101–107. doi:10.1016/j.trsl.2017.02.004
- Madiraju, A.K., Erion, D.M., Rahimi, Y., Zhang, X.-M., Braddock, D.T., Albright, R.A., *et al.*, 2014. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. *Nature.* 510: 542–546. doi:10.1038/nature13270
- Magkos, F., Hjorth, M.F., & Astrup, A., 2020. Diet and exercise in the prevention and treatment of type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* 16: 545–555. doi:10.1038/s41574-020-0381-5
- Maharani, A., Sujarwoto, Praveen, D., Oceandy, D., Tampubolon, G., & Patel, A., 2019. Cardiovascular disease risk factor prevalence and estimated 10-year cardiovascular risk scores in Indonesia: The SMARThealth Extend study. *PLoS One.* 14: e0215219. doi:10.1371/journal.pone.0215219

- Mahrooz, A., Parsanasab, H., Hashemi-Soteh, M.B., Kashi, Z., Bahar, A., Alizadeh, A., *et al.*, 2015. The role of clinical response to metformin in patients newly diagnosed with type 2 diabetes: a monotherapy study. *Clin. Exp. Med.* 15: 159–165. doi:10.1007/s10238-014-0283-8
- Maida, A., Lamont, B.J., Cao, X., & Drucker, D.J., 2011. Metformin regulates the incretin receptor axis via a pathway dependent on peroxisome proliferator-activated receptor- α in mice. *Diabetologia*. 54: 339–349. doi:10.1007/s00125-010-1937-z
- Malodobra-Mazur, M., Bednarska-Chabowska, D., Olewinski, R., Chmielecki, Z., Adamiec, R., & Dobosz, T., 2016. Single nucleotide polymorphisms in 5'-UTR of the SLC2A4 gene regulate solute carrier family 2 member 4 gene expression in visceral adipose tissue. *Gene*. 576: 499–504. doi:10.1016/j.gene.2015.10.067
- Maloney, A., Rosenstock, J., & Fonseca, V., 2019. A model-based meta-analysis of 24 antihyperglycemic drugs for type 2 diabetes: comparison of treatment effects at therapeutic doses. *Clin. Pharmacol. Ther.* 105: 1213-1223. doi:10.1002/cpt.1307
- Mambiya, M., Shang, M., Wang, Y., Li, Q., Liu, S., Yang, L., *et al.*, 2019. The play of genes and non-genetic factors on type 2 Ddabetes. *Front. Public Heal.* 17: 349. doi:10.3389/fpubh.2019.00349
- Marshall, S.M., 2017. 60 years of metformin use : a glance at the past and a look to the future. *Diabetologia*. 60: 1561–1565. doi:10.1007/s00125-017-4343-y
- McArdle, P.D., Greenfield, S.M., Rilstone, S.K., Narendran, P., Haque, M.S., & Gill, P.S., 2019. Carbohydrate restriction for glycaemic control in Type 2 diabetes: a systematic review and meta-analysis. *Diabet. Med.* 36: 335–348. doi:10.1111/dme.13862
- Mekary, R.A., 2019. Breakfast skipping and type 2 diabetes: where do we stand? *J. Nutr.* 149: 1-3. doi:10.1093/jn/nxy284
- Mekary, R.A., Giovannucci, E., Willett, W.C., Van Dam, R.M., & Hu, F.B., 2012. Eating patterns and type 2 diabetes risk in men: breakfast omission, eating frequency, and snacking. *Am. J. Clin. Nutr.* 95: 1182–1189. doi:10.3945/ajcn.111.028209
- Meng, S., Cao, J., He, Q., Xiong, L., Chang, E., Radovick, S., *et al.*, 2015. Metformin activates AMP-activated protein kinase by promoting formation of the $\alpha\beta\gamma$ heterotrimeric complex. *J. Biol. Chem.* 290: 3393–3802. doi:10.1074/jbc.M114.604421
- Mihardja, L., Soetrisno, U., & Soegondo, S., 2014. Prevalence and clinical profile of diabetes mellitus in productive aged urban Indonesians. *J. Diabetes Invest.* 5: 507–512. doi:10.1111/jdi.12177
- Miller, R.A., Chu, Q., Xie, J., Foretz, M., Viollet, B., & Birnbaum, M.J., 2013. Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. *Nature*. 494: 256–60. doi:10.1038/nature11808
- Mirzaei, M., Rahmaninan, M., Mirzaei, M., Nadjarzadeh, A., & Dehghani Tafti, A.A., 2020. Epidemiology of diabetes mellitus, pre-diabetes, undiagnosed and uncontrolled diabetes in Central Iran: Results from Yazd health study. *BMC Public Health*. 20: 166. doi:10.1186/s12889-020-8267-y
- Mokta, J.K., Ramesh, Sahai, A.K., Kaundal, P.K., & Mokta, K., 2018. Comparison of safety and efficacy of glimepiride-metformin and vildagliptin-metformin treatment in newly diagnosed type 2 diabetic patients. *J. Assoc. Physicians India*. 66: 30–35.
- Moon, J.S., & Won, K.C., 2015. Pancreatic α -Ccell dysfunction in type 2 diabetes: old kids on the block. *Diabetes Metab. J.* 39: 1–9. doi:10.4093/dmj.2015.39.1.1
- Mostafa-Hedeab, G., Mohamed, A.A., Thabet, G., Sabry, D., Salam, R.F., & Hassen, M.E., 2018. Effect of MATE 1, MATE 2 and OCT1 single nucleotide polymorphisms on metformin action in recently diagnosed Egyptian type-2 diabetic patients. *Biomed. Pharmacol. J.* 11: 149–157. doi:10.13005/bpj/1356
- Mottalib, A., Salsberg, V., Mohd-Yusof, B.N., Mohamed, W., Carolan, P., Pober, D.M., *et*

- al., 2018. Effects of nutrition therapy on HbA1c and cardiovascular disease risk factors in overweight and obese patients with type 2 diabetes. *Nutr. J.* 17. doi:10.1186/s12937-018-0351-0
- Mulherin, A.J., Oh, A.H., Kim, H., Grieco, A., Lauffer, L.M., & Brubaker, P.L., 2011. Mechanisms underlying metformin-induced secretion of glucagon-like peptide-1 from the intestinal L cell. *Endocrinology*. 152: 4610–4619. doi:10.1210/en.2011-1485
- Müller, J., Lips, K.S., Metzner, L., Neubert, R.H.H., Koepsell, H., & Brandsch, M., 2005. Drug specificity and intestinal membrane localization of human organic cation transporters (OCT). *Biochem. Pharmacol.* 70: 1851–1860. doi:10.1016/J.BCP.2005.09.011
- Mullugeta, Y., Chawla, R., Kebede, T., & Worku, Y., 2012. Dyslipidemia associated with poor glycemic control in type 2 diabetes mellitus and the protective effect of metformin supplementation. *Indian J. Clin. Biochem.* 27: 363–369. doi:10.1007/s12291-012-0225-8
- Musi, N., Hayashi, T., Fujii, N., Hirshman, M.F., Witters, L.A., & Goodyear, L.J., 2001. AMP-activated protein kinase activity and glucose uptake in rat skeletal muscle. *Am. J. Physiol. Metab.* 280: E677–E684. doi:10.1152/ajpendo.2001.280.5.E677
- Musi, N., Hirshman, M.F., Nygren, J., Svanfeldt, M., Bavenholm, P., Rooyackers, O., et al., 2002. Metformin increases AMP-activated protein kinase activity in skeletal muscle of subjects with type 2 diabetes. *Diabetes*. 51: 2074–2081.
- Nanditha, A., Ma, R.C.W., Ramachandran, A., Snehalatha, C., Chan, J.C.N., Chia, K.S., et al., 2016. Diabetes in Asia and the pacific: Implications for the global epidemic. *Diabetes Care*. 39: 472–485. doi:10.2337/dc15-1536
- National Cholesterol Education Program, 2001. High blood cholesterol ATP III guidelines at-a-glance quick desk reference. U.S.
- Nauck, M.A., & Meier, J.J., 2016. The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. *Lancet. Diabetes Endocrinol.* 4: 525–36. doi:10.1016/S2213-8587(15)00482-9
- Nies, A.T., Koepsell, H., Winter, S., Burk, O., Klein, K., Kerb, R., et al., 2009. Expression of organic cation transporters OCT1 (SLC22A1) and OCT3 (SLC22A3) is affected by genetic factors and cholestasis in human liver. *Hepatology*. 50: 1227–1240. doi:10.1002/hep.23103
- Nikolaos Papanas, E.M.& D.P.M., 2012. Metformin and heart failure: never say never again. *Expert Opin. Pharmacother.* 13: 1-8. doi:10.1517/14656566.2012.638283
- Ningrum, V.D.A., Ikawati, Z., Sadewa, A.H., & Ikhsan, Mr., 2016. Faktor pasien yang mempengaruhi respon glikemik penggunaan monoterapi metformin pada diabetes mellitus tipe 2. *Jurnal Manajemen dan Pelayanan Farmasi*, 6: 261–269. doi:10.22146/jmpf.355
- Nishida, C., Barba, C., Cavalli-Sforza, T., Cutter, J., Deurenberg, P., Darnton-Hill, I., et al., 2004. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 363: 157–163. doi:10.1016/S0140-6736(03)15268-3
- Ogurtsova, K., Da, J.D., Fernandes, R., Huang, Y., Linnenkamp, U., Guariguata, L., et al., 2017. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res. Clin. Pract.* 128: 40–50. doi:10.1016/j.diabres.2017.03.024
- Okemah, J., Peng, J., Quiñones, M., 2018. Addressing Clinical Inertia in Type 2 Diabetes Mellitus: A Review. 35: 1735-1745. *Adv. Ther.* doi:10.1007/s12325-018-0819-5
- Omar, S.M., Musa, I.R., ElSouli, A., & Adam, I., 2019. Prevalence, risk factors, and glycaemic control of type 2 diabetes mellitus in eastern Sudan: a community-based study. *Ther. Adv. Endocrinol. Metab.* 10: 2042018819860071. doi:10.1177/2042018819860071

- Ota, A., Kondo, N., Murayama, N., Tanabe, N., Shobugawa, Y., Kondo, K., 2016. Serum albumin levels and economic status in Japanese older adults. *PLoS One*. 11: e0155022. doi:10.1371/journal.pone.0155022
- Ormazabal, V., Nair, S., Elfeky, O., Aguayo, C., Salomon, C., & Zuñiga, F.A., 2018. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc. Diabetol.* 17: 122. doi:10.1186/s12933-018-0762-4
- Ouyang, J., Parakhia, R.A., & Ochs, R.S., 2011. Metformin activates AMP kinase through inhibition of AMP deaminase. *J. Biol. Chem.* 286: 1–11. doi:10.1074/jbc.M110.121806
- Owen, M.R., Doran, E., & Halestrap, A.P., 2000. Evidence that metformin exerts its anti-diabetics effects through inhibition of complex 1 of mitochondrial respiratory chain. *Biochem. Soc.* 348: 607–614. doi:10.1042/bj3480607
- Pagidipati, N.J., Zheng, Y., Green, J.B., McGuire, D.K., Mentz, R.J., Shah, S., *et al.*, 2020. Association of obesity with cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease: Insights from TECOS. *Am. Heart J.* 219: 47–57. doi:10.1016/j.ahj.2019.09.016
- Pantalone, K.M., Hobbs, T.M., Wells, B.J., Kong, S.X., Kattan, M.W., Bouchard, J., *et al.*, 2016. Changes in characteristics and treatment patterns of patients with newly diagnosed type 2 diabetes in a large United States integrated health system between 2008 and 2013. *Clin. Med. Insights Endocrinol. Diabetes.* 9: 23–30. doi:10.4137/CMED.S39761
- Papazafiropoulou, A., & Melidonis, A., 2019. Antidiabetic agents in patients with hepatic impairment. *World J. Meta-Analysis.* 7: 380–388. doi:10.13105/wjma.v7.i8.380
- Papazafiropoulou, A., Papanas, N., Melidonis, A., & Maltezos, E., 2017. Family history of type 2 diabetes: does having a diabetic parent increase the risk? *Curr. Diabetes Rev.* 13: 19–25. doi:10.2174/1573399812666151022143502
- Park, J.H., & Lee, Y.E., 2015. Effects of exercise on glycemic control in type 2 diabetes mellitus in Koreans: the fifth Korea national health and nutrition examination survey (KNHANES V). *J. Phys. Ther. Sci.* 27: 3559–3564. doi:10.1589/jpts.27.3559
- Pavkov, M.E., Knowler, W.C., Lemley, K. V., Mason, C.C., Myers, B.D., & Nelson, R.G., 2012. Early renal function decline in type 2 diabetes. *Clin. J. Am. Soc. Nephrol.* 7: 78–84. doi:10.2215/CJN.07610711
- Pawlyk, A.C., Giacomini, K.M., McKeon, C., Shuldiner, A.R., & Florez, J.C., 2014. Metformin pharmacogenomics: Current status and future directions. *Diabetes.* 63: 2590–2599. doi:10.2337/db13-1367
- Phung, O.J., Sobieraj, D.M., Engel, S.S., & Rajpathak, S.N., 2014. Early combination therapy for the treatment of type 2 diabetes mellitus: Systematic review and meta-analysis. *Diabetes, Obes. Metab.* 16: 410–417. doi:10.1111/dom.12233
- Polonsky, W.H., & Henry, R.R., 2016. Poor medication adherence in type 2 diabetes : recognizing the scope of the problem and its key contributors. *Patient Prefer. Adherence.* 10: 1299–1307.
- Poudel, R.R., 2013. Renal glucose handling in diabetes and sodium glucose cotransporter 2 inhibition. *Indian J. Endocrinol. Metab.* 17: 588–93. doi:10.4103/2230-8210.113725
- Prado, K.B., & Napierkowski, D., 2020. preventative strategies of atherosclerotic cardiovascular disease. *J. Nurse Pract.* 16: 253–257. doi:10.1016/j.nurpra.2019.09.020
- Pu, R., Shi, D., Gan, T., Ren, X., Ba, Y., Huo, Y., *et al.*, 2020. Effects of metformin in obesity treatment in different populations: a meta-analysis. *Ther. Adv. Endocrinol. Metab.* 11. doi:10.1177/2042018820926000
- Pubchem, 2018. Metformin | C4H11N5 - PubChem. <https://pubchem.ncbi.nlm.nih.gov/compound/metformin> (accessed 3.14.19).
- Rahimi, E., 2018. Physical activity and type 2 diabetes: A narrative review. *J. Phys. Act.*

- Rahmayani, R., Aman, A.K., & Safril, S., 2019. The association of insulin resistance and lipid profile ratio in metabolic syndrome. *Indones. J. Clin. Pathol. Med. Lab.* 25: 21–25.
- Ramachandran, A., 2014. Know the signs and symptoms of diabetes. *Indian J. Med. Res.* 140: 579–581.
- Ramadhan & Hanum, S., 2016. Kontrol glikemik pada penderita diabetes mellitus tipe 2 di Puskesmas Jayabaru Kota Banda Aceh. *Sel.* 3: 1–10.
- Randeria, S.N., Thomson, G.J.A., Nell, T.A., Roberts, T., Pretorius, E., 2019. Inflammatory cytokines in type 2 diabetes mellitus as facilitators of hypercoagulation and abnormal clot formation. *Cardiovasc. Diabetol.* 18: 72. doi:10.1186/s12933-019-0870-9
- Randrianarisoa, E., Lehn-Stefan, A., Krier, J., Böhm, A., Heni, M., Hrabě De Angelis, M., *et al.*, 2020. AMPK subunits harbor largely nonoverlapping genetic determinants for body fat mass, glucose metabolism, and cholesterol metabolism. *J. Clin. Endocrinol. Metab.* 105: dgz020. doi:10.1210/clinem/dgz020
- Rani, J., Mittal, I., Pramanik, A., Singh, N., Dube, N., Sharma, S., *et al.*, 2017. T2DiACoD: A gene atlas of type 2 diabetes mellitus associated complex disorders. *Sci. Rep.* 7: 1–21. doi:10.1038/s41598-017-07238-0
- Rasheed, M., Islam, N., & Mahjabeen, W., 2015. Factors associated with uncontrolled type 2 diabetes mellitus. *J. Islam. Med. Dent. Coll.* 4: 68–71.
- Rashid, M., Shahzad, M., Mahmood, S., & Khan, K., 2019. Variability in the therapeutic response of metformin treatment in patients with type 2 diabetes mellitus. *Pakistan J. Med. Sci.* 35: 71–76. doi:10.12669/pjms.35.1.100
- Rashid, M., Shahzad, M., Mahmood, S., & Khan, K., 2018. Variability in the therapeutic response of metformin treatment in patients with type 2 diabetes Mellitus. *Pakistan J. Med. Sci.* 35: 71–76. doi:10.12669/pjms.35.1.100
- Reiss, A.B., Glass, D.S., Voloshyna, I., Glass, A.D., Kasselmann, L.J., De Leon, J., 2020. Obesity and atherosclerosis: the exosome link. *Vessel Plus* 2020. 4: 19. doi:10.20517/2574-1209.2020.04
- Rena, G., Hardie, D.G., & Pearson, E.R., 2017. The mechanisms of action of metformin. *Diabetologia.* 60: 1577–1585. doi:10.1007/s00125-017-4342-z
- Rhee, E.J., 2015. Diabetes in Asians. *Endocrinol. Metab. (Seoul, Korea)* 30: 263–9. doi:10.3803/EnM.2015.30.3.263
- Rodriguez-Araujo, G., & Nakagami, H., 2018. Pathophysiology of cardiovascular disease in diabetes mellitus. *Cardiovasc. Endocrinol. Metab.* 7: 4–9. doi:10.1097/XCE.0000000000000141
- Rogacka, D., Audzeyenka, I., & Piwkowska, A., 2020. Regulation of podocytes function by AMP-activated protein kinase. *Arch. Biochem. Biophys.* 692: 108541. doi:10.1016/j.abb.2020.108541
- Roglic, G., Varghese, C., & Thamarangsi, T., 2016. Diabetes in South-East Asia: burden, gaps, challenges and ways forward. *WHO South-East Asia J. public Heal.* 5: 1–4. doi:10.4103/2224-3151.206546
- Rojas, L.B.A., & Gomes, M.B., 2013. Metformin: an old but still the best treatment for type 2 diabetes. *Diabetol. Metab. Syndr.* 5: 6. doi:10.1186/1758-5996-5-6
- Sadarang, R.A.I., 2021. Factors associated with quitting smoking in indonesia. *J. Prev. Med. Public Heal.* 54: 137–144. doi:10.3961/jpmph.20.293
- Sakane, N., Sato, J., Tsushita, K., Tsujii, S., Kotani, K., Tominaga, M., *et al.*, 2014. Effect of baseline HbA1c level on the development of diabetes by lifestyle intervention in primary healthcare settings: insights from subanalysis of the Japan Diabetes Prevention Program. *BMJ Open Diabetes Res. Care* 2: e000003. doi:10.1136/bmjdr-2013-000003
- Sattar, N., Rawshani, A., Franzén, S., Rawshani, A., Svensson, A.M., Rosengren, A., *et al.*,

2019. Age at diagnosis of type 2 diabetes mellitus and associations with cardiovascular and mortality risks: findings from the Swedish National Diabetes Registry. *Circulation*. 139: 2228–2237. doi:10.1161/CIRCULATIONAHA.118.037885
- Scheen, A.J., 1996. Clinical pharmacokinetics of metformin. *Clin. Pharmacokinet.* 30: 359–371. doi:10.2165/00003088-199630050-00003
- Schwab, C., Paar, M., Fengler, V.H., Ivastinovic, D., Haas, A., Seidel, G., *et al.*, 2020. Gender differences in albumin and ascorbic acid in the vitreous antioxidant system. *Free Radic. Biol. Med.* 146: 257–263. doi:10.1016/j.freeradbiomed.2019.11.008
- Schwartz, S.S., Epstein, S., Corkey, B.E., Grant, S.F.A., Gavin, J.R., Aguilar, R.B., 2016. The time is right for a new classification system for diabetes: Rationale and implications of the β -cell-centric classification schema. *Diabetes Care*. 39: 179–186. doi:10.2337/dc15-1585
- Setyopranoto, I., Bayuangga, H.F., Panggabean, A.S., Alifaningdyah, S., Lazuardi, L., Dewi, F.S.T., *et al.*, 2019. Prevalence of stroke and associated risk factors in sleman district of Yogyakarta Special Region, Indonesia. *Stroke Res. Treat.* 2019: 2642458. doi:10.1155/2019/2642458
- Shen, J.-Z., Ge, W.-H., Fang, Y., & Liu, H., 2017. A novel polymorphism in protein kinase AMP-activated catalytic subunit alpha 2 (PRKAA2) is associated with type 2 diabetes in the Han Chinese population. *J. Diabetes*. 9: 606–612. doi:10.1111/1753-0407.12449
- Shpakov, A.O., Derkach, K. V., & Bernstein, L.M., 2015. Brain signaling systems in the type 2 diabetes and metabolic syndrome: promising target to treat and prevent these diseases. *Futur. Sci. OA*. 1: 25. doi:10.4155/FSO.15.23
- Singhai, K., Swami, M.K., Nebhinani, N., Rastogi, A., & Jude, E., 2020. Psychological adaptive difficulties and their management during COVID-19 pandemic in people with diabetes mellitus. *Diabetes Metab. Syndr. Clin. Res. Rev.* 14: 1603–1605. doi:10.1016/j.dsx.2020.08.025
- Sivitz, W., Phillips, L.S., Fortmann, S.P., Wexler, D.J., Camp, A.W., Tiktin, M., *et al.*, 2018. Changes in hba1c with optimization of metformin dosage in the GRADE cohort. *Diabetes* 67: 116–LB. doi:10.2337/db18-116-lb
- Skyler, J.S., Bakris, G.L., Bonifacio, E., Darsow, T., Eckel, R.H., Groop, L., *et al.*, 2017. Differentiation of diabetes by pathophysiology, natural history, and prognosis. *Diabetes*. 66: 241–255. doi:10.2337/db16-0806
- Sliwiska-Mosson, M., & Milnerowicz, H., 2017. The impact of smoking on the development of diabetes and its complications. *Diabetes Vasc. Dis. Res.* 14: 265–276. doi:10.1177/1479164117701876
- Soelistijo, S.A., Lindarto, D., Decroli, E., Permana, H., Sucipto, K.W., Kusnadi, Y., *et al.*, 2019. Pedoman pengelolaan dan pencegahan diabetes melitus tipe 2 dewasa di Indonesia 2019. *Perkumpulan Endokrinol. Indones.* 1–117.
- Sonuga, O.O., Abbiyesuku, F.M., Adedapo, K.S., & Sonuga, A.A., 2019. Insulin resistance index and proatherogenic lipid indices in the offspring of people with diabetes. *Int. J. Diabetes Metab.* 25: 11–18. doi:10.1159/000497079
- Soraya, H., Clanachan, A.S., Rameshrad, M., Maleki-Dizaji, N., Ghazi-Khansari, M., & Garjani, A., 2014. Chronic treatment with metformin suppresses toll-like receptor 4 signaling and attenuates left ventricular dysfunction following myocardial infarction. *Eur. J. Pharmacol.* 737: 77–84. doi:10.1016/j.ejphar.2014.05.003
- Spencer-Jones, N.J., Ge, D., Snieder, H., Perks, U., Swaminathan, R., Spector, T.D., *et al.*, 2006. AMP-kinase α 2 subunit gene PRKAA2 variants are associated with total cholesterol, low-density lipoprotein-cholesterol and high-density lipoprotein-cholesterol

- in normal women. *J. Med. Genet.* 43: 936–942. doi:10.1136/jmg.2006.041988
- Sumitani, S., Morita, S., Deguchi, R., Hirai, K., Mukai, K., Utsu, Y., *et al.*, 2015. Metformin decreases glycated albumin to glycated haemoglobin ratio in patients with newly diagnosed type 2 diabetes. *Ann. Clin. Biochem.* 52: 76–81. doi:10.1177/0004563214522984
- Sun, D., Zhou, T., Heianza, Y., Li, X., Fan, M., Fonseca, V.A., *et al.*, 2019. Type 2 diabetes and hypertension: A study on bidirectional causality. *Circ. Res.* 124: 930–937. doi:10.1161/CIRCRESAHA.118.314487
- Sun, G.Z., Ye, N., Wu, S.J., Zhou, Y., Sun, Y.X., 2019. 10-year ASCVD risk is positively correlated with depressive symptoms in a large general population. *BMC Psychiatry.* 19: 125. doi:10.1186/s12888-019-2114-7
- Sun, M.W., Lee, J.Y., de Bakker, P.I.W., Burt, N.P., Almgren, P., Råstam, L., *et al.*, 2006. Haplotype structures and large-scale association testing of the 5' AMP-activated protein kinase genes PRKAA2, PRKAB1, and PRKAB2 [corrected] with type 2 diabetes. *Diabetes.* 55: 849–855. doi:10.2337/DIABETES.55.03.06.DB05-1418
- Tancredi, M., Rosengren, A., Svensson, A.-M., Kosiborod, M., Pivodic, A., Gudbjörnsdottir, S., *et al.*, 2015. Excess mortality among persons with type 2 diabetes. *N. Engl. J. Med.* 373: 1720–1732. doi:10.1056/NEJMoa1504347
- Tao, J., Gao, L., Liu, Q., Dong, K., Huang, J., Peng, X., *et al.*, 2020. Factors contributing to glycemic control in diabetes mellitus patients complying with home quarantine during the coronavirus disease 2019 (COVID-19) epidemic. *Diabetes Res. Clin. Pract.* 170: 108514. doi:10.1016/j.diabres.2020.108514
- The ADVANCE Collaborative Group, 2008. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N. Engl. J. Med.* 358: 2560–2572. doi:10.1056/NEJMoa0802987
- Tiwari, S., Bhattarai, A., Acharya, R.P., Prasad, P.N., 2015. The effects of metformin use on body mass index: A prospective study. *Ann. Clin. Chem. Lab. Med.* 1: 16–20. doi:10.3126/acclm.v1i1.12309
- Todd, J.N., & Florez, J.C., 2014. An update on the pharmacogenomics of metformin: progress, problems and potential. *Pharmacogenomics.* 15: 529–539. doi:10.2217/pgs.14.21
- Topel, M.L., Shen, J., Morris, A.A., Al Mheid, I., Sher, S., Dunbar, S.B., *et al.*, 2018. Comparisons of the Framingham and Pooled Cohort Equation Risk Scores for detecting subclinical vascular disease in Blacks versus Whites. *Am. J. Cardiol.* 121: 564–569. doi:10.1016/j.amjcard.2017.11.031
- Tseng, C.H., 2018. Metformin and risk of hypertension in taiwanese patients with type 2 diabetes mellitus. *J. Am. Heart Assoc.* 7: e008860. doi:10.1161/JAHA.118.008860
- Tsimihodimos, V., Gonzalez-Villalpando, C., Meigs, J.B., & Ferrannini, E., 2018. Hypertension and diabetes mellitus coprediction and time trajectories. *Hypertension.* 71: 422–428. doi:10.1161/HYPERTENSIONAHA.117.10546
- Tsuchiya, A., Kanno, T., & Nishizaki, T., 2013. Diacylglycerol promotes GLUT4 translocation to the cell surface in a PKC ϵ -dependent and PKC λ / ι and ζ -independent manner. *Life Sci.* 93: 240–246. doi:10.1016/J.LFS.2013.06.014
- Turban, S., Stretton, C., Drouin, O., Green, C.J., Watson, M.L., Gray, A., *et al.*, 2012. Defining the contribution of AMP-activated protein kinase (AMPK) and protein kinase C (PKC) in regulation of glucose uptake by metformin in skeletal muscle cells. *J. Biol. Chem.* 287: 20088–20099. doi:10.1074/jbc.M111.330746
- Utomo & Marunduh, S., 2015. Kadar HbA1C pada pasien diabetes melitus tipe 2 di Puskesmas Bahu Kecamatan Malalayang. *eBiomedik* 3: 3–11.
- Viollet, B., Andreelli, F., Jørgensen, S.B., Perrin, C., Flamez, D., Mu, J., *et al.*, 2003.

- Physiological role of AMP-activated protein kinase (AMPK): insights from knockout mouse models. *Biochem. Soc. Trans.* 31: 216–219. doi:10.1042/
- Wan, K.S., Moy, F.M., Yusof, K.M., Mustapha, F.I., Ali, Z.M., Hairi, N.N., 2020. Clinical inertia in type 2 diabetes management in a middle-income country: A retrospective cohort study. *PLoS One* 15: e0240531. doi:10.1371/journal.pone.0240531
- Wang, J., Li, X., Sun, X., Li, G., Sun, J., Ye, Y., *et al.*, 2018. Activation of AMPK by simvastatin inhibited breast tumor angiogenesis via impeding HIF-1 α -induced pro-angiogenic factor. *Cancer Sci.* 109: 1627–1637. doi:10.1111/cas.13570
- Wang, P.Y., Fang, J.C., Gao, Z.H., Zhang, C., & Xie, S.Y., 2016. Higher intake of fruits, vegetables or their fiber reduces the risk of type 2 diabetes: A meta-analysis. *J. Diabetes Investig.* 7: 56–69. doi:10.1111/jdi.12376
- Wang, Y., An, H., Liu, T., Qin, C., Sesaki, H., Guo, S., *et al.*, 2019. Metformin improves mitochondrial respiratory activity through activation of AMPK. *Cell Rep.* 29: 1511–1523.e5. doi:10.1016/j.celrep.2019.09.070
- Weaving, G., Batstone, G.F., Jones, R.G., 2016. Age and sex variation in serum albumin concentration: an observational study. *Ann. Clin. Biochem.* 53: 106–111. doi:10.1177/0004563215593561
- Whiting, D.R., Guariguata, L., Weil, C., & Shaw, J., 2011. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res. Clin. Pract.* 94: 311–21. doi:10.1016/j.diabres.2011.10.029
- Williams, L.K., Padhukasahasram, B., Ahmedani, B.K., Peterson, E.L., Wells, K.E., González Burchard, E., *et al.*, 2014. Differing effects of metformin on glycemic control by race-ethnicity. *J. Clin. Endocrinol. Metab.* 99: 3160–3168. doi:10.1210/jc.2014-1539
- Willows, R., Sanders, M.J., Xiao, B., Patel, B.R., Martin, S.R., Read, J., *et al.*, 2017. Phosphorylation of AMPK by upstream kinases is required for activity in mammalian cells. *Biochem. J.* 1: BCJ20170458. doi:10.1042/BCJ20170458
- Wondmunkun, Y.T., 2020. Obesity, insulin resistance, and type 2 diabetes: Associations and therapeutic implications. *Diabetes, Metab. Syndr. Obes. Targets Ther.* 13: 3611-3616. doi:10.2147/DMSO.S275898
- World Health Organization, 2018. Diabetes. *World Heal. Organ.* <http://www.who.int/news-room/fact-sheets/detail/diabetes> (accessed 11.26.18).
- World Health Organization, 2019. Country profile Indonesia Summary of MPOWER measures in Indonesia. https://www.who.int/tobacco/surveillance/policy/country_profile/idn.pdf (accessed 06.26.21).
- Wu, Y., Ding, Y., Tanaka, Y., & Zhang, W., 2014. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. *Int. J. Med. Sci.* 11: 1185–200. doi:10.7150/ijms.10001
- Wulffe, M.G., Kooy, A., Zeeuw, D., Stehouwer, C.D.A., & Gansevoort, R.T., 2004. The effect of metformin on blood pressure, plasma cholesterol and triglycerides in type 2 diabetes mellitus: a systematic review. *J. Intern. Med.* 256: 1–14. doi:10.1111/j.1365-2796.2004.01328.x
- Xie, Z., Lau, K., Eby, B., Lozano, P., He, C., Pennington, B., *et al.*, 2011. Improvement of cardiac functions by chronic metformin treatment is associated with enhanced cardiac autophagy in diabetic OVE26 mice. *Diabetes.* 60: 1770–1778. doi:10.2337/db10-0351
- Xu, X., Li, J., Lu, Z., Fasserr, J., Zhu, G., Tao, Y., *et al.*, 2014. Metformin protects against systolic overload-induced heart failure independent of AMP-activated protein kinase α 2. *Hypertension.* 63: 723–728. doi:10.1161/HYPERTENSIONAHA.113.02619.
- Yagihashi, S., Inaba, W., & Mizukami, H., 2016. Dynamic pathology of islet endocrine cells in type 2 diabetes: β -Cell growth, death, regeneration and their clinical implications. *J.*

- Diabetes Investig.* 7: 155–165. doi:10.1111/jdi.12424
- Yang, C.T., Yang, C.Y., Ou, H.T., Kuo, S., 2020. Comparative cardiovascular safety of GLP-1 receptor agonists versus other glucose-lowering agents in real-world patients with type 2 diabetes: A nationwide population-based cohort study. *Cardiovasc. Diabetol.* 19: 1–10. doi:10.1186/s12933-020-01053-0
- Yang, D., Yang, Y., Li, Y., & Han, R., 2019. Physical exercise as therapy for type 2 diabetes mellitus: from mechanism to orientation. *Ann. Nutr. Metab.* 74: 313–321. doi:10.1159/000500110
- Yao, F., Zhang, M., & Chen, L., 2016. 5'-Monophosphate-activated protein kinase (AMPK) improves autophagic activity in diabetes and diabetic complications. *Acta Pharm. Sin. B* 6: 20–25. doi:10.1016/j.apsb.2015.07.009
- Yoon, K.H., Shin, J.A., Kwon, H.S., Lee, S.H., Min, K.W., Ahn, Y.B., *et al.*, 2011. Comparison of the efficacy of glimepiride, metformin, and rosiglitazone monotherapy in Korean drug-naïve type 2 diabetic patients: The practical evidence of antidiabetic monotherapy study. *Diabetes Metab. J.* 35: 26–33. doi:10.4093/dmj.2011.35.1.26
- Young Jeon, J., Jin Lee, S., Lee, S., Jin Kim, S., Jin Han, S., Jin Kim, H., *et al.*, 2018. Failure of monotherapy in clinical practice in patients with type 2 diabetes: The Korean National Diabetes Program. *J. Diabetes Investig.* 9: 1144–1152. doi:10.1111/jdi.12801
- Yu, S., Schwab, P., Bian, B., Radican, L., & Tunceli, K., 2016. Use of add-on treatment to metformin monotherapy for patients with type 2 diabetes and suboptimal glycemic control: A U.S. database study. *J. Manag. Care Spec. Pharm.* 22: 272–280. doi:10.18553/jmcp.2016.22.3.272
- Zhang, L., Chen, S., Deng, A., Liu, X., Liang, Y., Shao, X., *et al.*, 2015. Association between lipid ratios and insulin resistance in a Chinese population. *PLoS One.* 10: e0116110. doi:10.1371/journal.pone.0116110
- Zhou, G., Myers, R., Li, Y., Chen, Y., Shen, X., Fenyk-Melody, J., *et al.*, 2001. Role of AMP-activated protein kinase in mechanism of metformin action. *J. Clin. Invest.* 108: 1167–1174. doi:10.1172/JCI13505
- Zhou, K., Donnelly, L., Yang, J., Li, M., Deshmukh, H., Van Zuydam, N., A *et al.*, 2014. Heritability of variation in glycaemic response to metformin: a genome-wide complex trait analysis. *Lancet Diabetes Endocrinol.* 2: 481–7. doi:10.1016/S2213-8587(14)70050-6
- Zhou, M., Xia, L., & Wang, J., 2007. Metformin transport by a newly cloned proton-stimulated organic cation transporter (plasma membrane monoamine transporter) expressed in human intestine. *Drug Metab. Dispos.* 35: 1956–62. doi:10.1124/dmd.107.015495
- Zhou, T., Hu, Z., Yang, S., Sun, L., Yu, Z., Wang, G., 2018. Role of adaptive and innate immunity in type 2 diabetes mellitus. *J. Diabetes Res.* 2018: 7457269. doi:10.1155/2018/7457269
- Zhu, H., Zhu, S., Zhang, X., Guo, Y., Shi, Y., Chen, Z., *et al.*, 2013. Comparative efficacy of glimepiride and metformin in monotherapy of type 2 diabetes mellitus: Meta-analysis of randomized controlled trials. *Diabetol. Metab. Syndr.* 5: 70. doi:10.1186/1758-5996-5-70