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Nutritional intake of micronutrient and macronutrient and type 2 diabetes: machine learning schemes

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Abstract

Background Diabetes mellitus, an endocrine system disease, is a common disease involving many patients worldwide. Many studies are performed to evaluate the correlation between micronutrients/macronutrients on diabetes but few of them have a high statistical population and a long follow-up period. We aimed to investigate the relationship between intake of macro/micronutrients and the incidence of type 2 diabetes (T2D) using logistic regression (LR) and a decision tree (DT) algorithm for machine learning.

Method Our research explores supervised machine learning models to identify T2D patients using the Mashhad Cohort Study dataset. The study population comprised 9704 individuals aged 35–65 years were enrolled regarding their T2D status, and those with T2D history. 15% of individuals are diabetic and 85% of them are non-diabetic. For ten years (until 2020), the participants in the study were monitored to determine the incidence of T2D. LR is a statistical model applied in dichotomous response variable modeling. All data were analyzed by SPSS (Version 22) and SAS JMP software.

Result Nutritional intake in the T2D group showed that potassium, calcium, magnesium, zinc, iodine, carotene, vitamin D, tryptophan, and vitamin B12 had an inverse correlation with the incidence of diabetes ($p < 0.05$). While phosphate, iron, and chloride had a positive relationship with the risk of T2D ($p < 0.05$). Also, the T2D group significantly had higher carbohydrate and protein intake (p-value < 0.05).

Conclusion Machine learning models can identify T2D risk using questionnaires and blood samples. These have implications for electronic health records that can be explored further.

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Highlights

- Nutritional intake in the T2D group showed that potassium, calcium, magnesium, zinc, iodine, carotene, vitamin D, tryptophan, and vitamin B12 had an inverse correlation with the incidence of diabetes.
- The T2D group significantly had higher carbohydrate and protein intake.

Keywords Data mining, Diabetes, Macro/Micronutrients, Decision tree

Introduction

Diabetes mellitus is an endocrine system disease that [1] is known as a group of metabolic conditions caused by impaired insulin secretion, insufficient insulin action, or both [2]. Diabetes is a significant public health issue in the U.S. and around the world; it has been divided into four categories: type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes (GD), and specific types of diabetes (e.g. monogenic diabetes syndromes and drug or chemical-induced diabetes) [3–5]. Type 2 diabetes mellitus (T2DM) is rising is relation to urbanization, population aging, and related lifestyle changes, especially in people over 65 [6]. Adults with diabetes were anticipated to number 415 million worldwide in 2015, and by 2040, that number will increase to 642 million [7, 8]. The national Coronary Artery Disease (CAD) risk factors monitoring report estimates that among Iranians aged 15 to 64, the prevalence of diabetes was 8.7% in overall, with nearly half (4.1%) of those patients were newly diagnosed cases [9]. Also, in 2019, a 70% increase compared to 2000 is one of the top 10 causes of death worldwide [10]. The prevalence of diabetes is estimated to be 536 million people in the age group of 20 to 79 years globally (1 in 10 adults) in 2021. It is further predicted that the percentage of adults with diabetes will increase to more than 46% (783 million) by 2045 [11]. Total economic costs for diabetes include direct costs from medical care and indirect costs (e.g., mortality, dropout), estimated to increase from $1.32 trillion in 2015 to $2.12 trillion by 2030 [12]. The pooled average annual treatment cost per diabetic patient was $255 in Iran [13].

Some research has shown the role of macronutrients and micronutrient intake in the incidence of diabetes [14, 15]. Also, low vitamin D status and calcium as micronutrients may be negatively related to T2D prevalence [16]. However, some studies have stated that there were no significant differences between vitamin D intake and the incidence of diabetes [17]. Certain research also suggested that vitamin C supplementation can reduce hyperglycemia [18]. A recent study in the United States showed that macronutrient intake was a predictive factor for insulin resistance and higher carbohydrate consumption was positively related to insulin resistance [19]. A previous meta-analysis of literature observed that higher-fiber diets could lead to reducing the risk of premature mortality in adults with diabetes [20]. There are few studies about the association between iodine intake and the incidence of T2D [21].

Having a proper diet that includes all the essential macro/micronutrient is one of the main steps in managing diabetes and controlling blood sugar. However, limited studies have been performed to investigate the relationship between the intake of some macro/micronutrients and the incidence of T2D. Moreover, most research in Asia has been conducted using small samples or short follow-up times to indicate the relationship between nutritional factors and T2D. Therefore, the present study was performed to investigate the relationship between levels of macro/micronutrients and the incidence of T2D using logistic regression (LR) and a decision tree (DT) algorithm for machine learning.

Methods

Participants

The participants in this cohort study were recruited from Mashhad Stroke and Heart Atherosclerotic disorders (MASHAD) Study, Mashhad, Iran [22]. Nine thousand seven hundred four (9704) individuals aged 35–65 years were enrolled regarding their T2D status. T2D was defined as a fasting blood glucose (FBG) ≥ 126 mg/dl or being treated with available oral hypoglycemic medications or insulin. After cleaning and balancing data, we had 9000 individuals in this study. The study started in 2010, and the subjects were followed up for ten years (to 2020) to determine the T2D incidents. All the participants consented to take part in the study by signing written informed consent. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences (MUMS) (Fig. 3).

Blood sampling

According to a standard protocol, all blood samples were taken from patients' antecubital veins between 8 and 10 am, after 12 h of fasting, in a setting position. The samples were collected in 20 ml vacuum tubes and centrifuged 30–45 min past collection to separate the serum and plasma, and later sent to Bu Ali Research Institute, Mashhad, for laboratory examinations. The details of laboratory measurements and cut-offs are explained in the baseline report of the MASHAD cohort study [22].

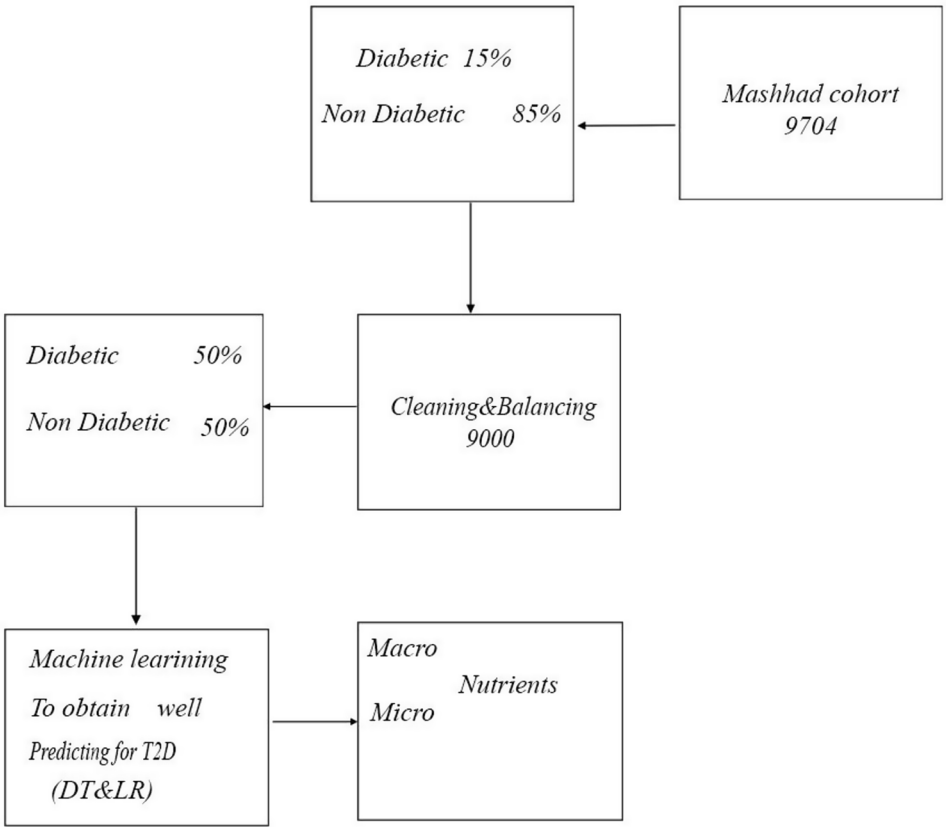

Fig. 3 Diagram of this study

Statistical analysis

The collected field data were transferred to the data banks with Microsoft visual studio, managed using NET software. The values with normal distribution in this study are reported as mean ± Standard Deviation (SD). Two independent sample t-tests were conducted to analyze participants' demographic and clinical data. All data were analyzed by SPSS (Version 22) and SAS JMP Pro (Version 13) softwares. The data with a p-value < 0.05 are considered statistically significant in this study. A chi-square test was performed to evaluate the significance of each factor in T2D incidents.

Decision tree modeling (DT)

Data mining methods are artificial intelligence analysis methods designed to extract hidden knowledge in large data sets. Decision Tree (DT) is particularly of service in data classification, widely used in medical fields due to its simplicity and clarity. The DT consists of nodes and branches, each representing a data section. The root node manifests the total records' subdivisions into two or more exclusive sets. The internal nodes, connecting the root and leaf nodes, act as test cases for some attributes, producing and predicting the results later displayed in leaf nodes. The final results are divided into target groups of leaf nodes. Each branch indicates the chance of placing new data/observation in target groups, emanated from the root and internal nodes. DT algorithm used the Gini impurity index to select the best variable:

$$Gini\,(D) = 1 - \sum_{i=1}^{m} P_i^2,$$

where P_i is the probability that a record in D belongs to the class C_i and is estimated by $|C_i, D|/|D$ [23]. DT aims to evaluate the predictor variables in order to develop a predictor model. This study performed a DT algorithm to classify the T2D related data and predict T2D incidents based on various risk factors. In the training phase of DT, the Gini index was applied to select the significant variables, and the final tree was obtained after pruning.

Logistic regression (LR)

Logistic regression (LR) is a statistical model applied in dichotomous response variable modeling. It investigates the effect of explanatory variables on the response variable and indicates the probability of assigning a new observation or data to each response variable group. The main advantage of LR is providing an appropriate direct or inverse relationship between the inputs/ explanatory

variables and the response variable, in addition to its high flexibility [24]. LR was performed with T2D incidents as the response variable and nutritional factors (Selenium, Magnesium, Potassium, Thiamin, Phosphate, Vitamin C, Manganese, Riboflavin, Carotene, Vitamin D, Iron, Iodine, Vitamin B12, Copper, Tryptophan, Folate, Calcium, Zinc, Niacin, Retinol, Chloride, Sodium, Fiber, Saturated fatty acid (satfat), Mono unsaturated fatty acid (monofat), Poly unsaturated fatty acid (polyufat), Trans fatty acid (transfat), Cholesterol, Protein, Water, Carbohydrate) as input variables.

Table 1 Summary of the participants' demographic characteristics

Variables	Diabetic ($n=4500$)	Non-Diabetic ($n=4500$)	*P*-value***
Age	52.18 ± 7.54*	48.00 ± 8.17	< 0.001
Sex Female Male	2825(62.77%)** 1675(37.22%0	2662(59.15%) 1838(40.84%)	< 0.001
Selenium	38.20 ± 29.60	37.21 ± 26.14	< 0.001
Magnesium	265.28 ± 93.23	246.52 ± 89.96	< 0.001
Potassium	3106.01 ± 1046.68	2778.54 ± 930.11	< 0.001
Thiamin	1.80 ± 0.52	1.77 ± 0.53	< 0.001
Phosphate	1387.73 ± 391.75	1296.43 ± 330.01	< 0.001
Vitamin C	97.04 ± 86.88	89.44 ± 86.75	< 0.001
Manganese	4.00 ± 1.48	4.08 ± 1.71	0.073
Riboflavin	2.21 ± 0.91	2.10 ± 0.89	< 0.001
Carotene	2959.01 ± 3608.26	2272.58 ± 2879.93	< 0.001
Vitamin D	2.22 ± 3.48	1.95 ± 5.08	< 0.001
Iron	11.73 ± 6.15	10.78 ± 5.19	< 0.001
Iodine	126.55 ± 106.67	108.18 ± 83.23	< 0.001
Vitamin B12	3.40 ± 9.28	3.04 ± 9.02	0.082
Copper	2.00 ± 1.31	2.00 ± 1.41	0.249
Tryptophan	15.83 ± 5.03	14.59 ± 4.04	< 0.001
Folate	255.89 ± 132.53	253.67 ± 159.64	0.001
Calcium	917.57 ± 423.39	834.10 ± 326.59	< 0.001
Zinc	9.77 ± 3.06	9.22 ± 2.83	< 0.001
Niacin	18.54 ± 11.69	16.72 ± 8.63	< 0.001
Retinol	431.54 ± 2254.48	451.49 ± 2426.52	0.560
Chloride	6826.99 ± 15281.97	4148.01 ± 11791.76	< 0.001
Sodium	4680.28 ± 9483.49	3118.03 ± 7418.20	< 0.001
Fiber	17.79 ± 9.70	16.98 ± 8.83	< 0.001
Saturated fatty acid (satfat)	18.57 ± 6.50	18.30 ± 7.12	0.01
Mono unsaturated fatty acid (monofat)	20.35 ± 7.04	19.72 ± 6.85	< 0.001
Poly unsaturated fatty acid (polyufat)	26.17 ± 13.88	23.76 ± 12.28	< 0.001
Trans fatty acid (transfat)	1.80 ± 0.67	1.79 ± 0.65	0.181
Cholesterol	233.95 ± 175.69	228.65 ± 196.02	0.189
Protein	75.33 ± 25.25	68.81 ± 20.60	< 0.001
Water	1574.17 ± 590.91	1492.85 ± 580.19	< 0.001
Carbohydrate	225.36 ± 55.57	240.26 ± 54.28	< 0.001

*Mean ± Sd

**n(%)

***P-value based on 2 sample t-test for Mean ± Sd and Chi-sq test for frequency (%). Significant at level of 0.05

Results

Characteristics of the participants

Table 1 summarizes the demographic and clinical characteristics of the study population. Of 9000 initial study participants, 4500 individuals (50%) developed T2D through the follow-up period, and 4500 (50%) remained non-diabetic. The female population was generally higher in both diabetic and non-diabetic groups (62.77% and 59.15%, respectively). The mean age of T2D cases was significantly older than that of the non-diabetic group (52.18 ± 7.54 vs. 48.00 ± 8.17, p-value < 0.001).

Relationship of nutritional factors with T2D incidents

Table 1 provides the results of the two performed independent t-tests to compare intakes of several nutritional micronutrient and macronutrient factors among the study participants. In micronutrient factors, the T2D case group had significantly higher selenium, magnesium, potassium, thiamin, phosphate, vitamin C, riboflavin, carotene, vitamin D, iron, iodine, tryptophan, folate, calcium, zinc, niacin, chloride, sodium in comparison with non-diabetic group (p-values < 0.05). However, retinol and copper were lower in diabetic cases (p-value = 0.560, 0.249, accordingly). Manganese and vitamin B12 marked no significant difference between the study groups. Whereas in macronutrient factors the T2D case group compared to the non-diabetic had significantly higher, protein, polyunsaturated fatty acid (polyufat), monounsaturated fatty acid (mono fat), saturated fatty acid (sat fat), fiber, water and carbohydrate (p-values < 0.05). There was no significant difference between T2D and non-diabetic groups in trance fatty acid (trans fat) and cholesterol (p-values = 0.181, 0.189).

Logistic regression modeling (LR)

According to the data mining analysis results in Table 2 (P-Value and LogWorth), potassium, tryptophan, sodium, chloride, phosphate, carotene, iodine, vitamin B12, iron, calcium, riboflavin, vitamin D, zinc and magnesium as micronutrients nutritional factors had a significant association with T2D incidents (p-value < 0.05). Potassium and tryptophan had the highest correlation with T2D development among the analyzed micronutrient nutritional factors. Our LR modeling indicated no significant relationship between other investigated nutritional factors and T2D.

Also, Table 2 lists the parameter estimates and the unit odds ratios for all significant micronutrient nutritional factors. Considering the achieved estimates through the LR model in Table 2, zinc and tryptophan represent the

Table 2 Parameter estimates of LR model and unit odds ratio for diabetes/non-diabetic by micronutrient nutritional factors

Term	Estimate	Std Error	*P*-Value	Unit Odds Ratio	Log-Worth
Intercept	-1.8237	0.1652	---------	---------	---------
Sodium	0.00062	0.0001	< 0.0001	1.0006	9.027
Potassium	0.00043	4.9768e-5	< 0.0001	1.0004	18.068
Calcium	0.00066	0.0001	0.0002	1.0006	3.726
Magnesium	0.00160	0.0007	0.0340	1.0016	1.471
Phosphate	-0.0016	0.0003	< 0.0001	0.9983	7.100
Iron	-0.0368	0.0097	0.0002	0.9637	3.882
Zinc	0.0418	0.0145	0.0040	1.0426	2.388
Chloride	-0.0004	6.8912e-5	< 0.0001	0.9995	8.568
Iodine	0.0024	0.0006	< 0.0001	1.0024	4.259
Carotene	6.59415e-5	1.3756e-5	< 0.0001	1.0001	6.100
Vitamin D	0.0323	0.0113	0.0045	1.0328	2.454
Riboflavin	-0.3540	0.0973	0.0003	0.7018	3.611
Tryptophan	0.1018	0.0127	< 0.0001	1.1071	15.475
Vitamin B12	0.0311	0.0080	0.0001	1.0316	3.972

Estimate: the coefficients of logistic regression

Std Error: used for testing whether the parameter is significantly different from 0

P-Value: indicate the probability of observing the coefficient value

Odds Ratio: the probability that the event occurs divided by the probability that the event does not occur. Odds ratios that are greater than 1 indicate that the event is more likely to occur as the predictor increases. Odds ratios that are less than 1 indicate that the event is less likely to occur as the predictor increases

Logworth =-log10(p-value)

Table 3 Parameter estimates of LR model and unit odds ratio for diabetes/non-diabetic by macronutrient nutritional factors

Term	Estimate	Std Error	*P*-Value	Unit Odds Ratio	Log-Worth
Intercept	2.4849	0.4884	-------	----------	---------
Water	0.0003	5.1027e-5	< 0.0001	1.0003	12.927
Protein	0.0098	0.0016	< 0.0001	1.0099	8.853
Carbohydrate	-0.0118	0.0011	< 0.0001	0.9881	25.677
Fiber	0.0084	0.0032	0.0100	1.0084	2.008
Sat fat	-0.0243	0.0056	< 0.0001	0.9759	4.783
Mono fat	-0.0274	0.0082	0.0009	0.9729	3.040
Cholesterol	-0.0008	0.0001	< 0.0001	0.9991	5.776

Estimate: the coefficients of logistic regression

Std Error: used for testing whether the parameter is significantly different from 0

P-Value: indicate the probability of observing the coefficient value

Odds Ratio: the probability that the event occurs divided by the probability that the event does not occur. Odds ratios that are greater than 1 indicate that the event is more likely to occur as the predictor increases. Odds ratios that are less than 1 indicate that the event is less likely to occur as the predictor increases

Logworth =-log10(p-value)

most appropriate estimates for non-T2D incidents (zinc estimate = 0.041 and tryptophan = 0.101, respectively). For unit odds ratio we can interpret that, the tryptophan variable has been identified as the most remarkable due to its high OR in the LR model. With an increase of one unit of tryptophan, the chance of classification in the non-T2D group increased 1.107 times. However, represented an odd ratio lower than 1 in this evaluation (OR = 0.7), indicating that a decrease of one unit of riboflavin is associated with an increase in the odds of non-T2D occurrence. Prediction formula for T2D is given in Appendix.

The sign of regression coefficients (LR estimates) represents the reverse of the association between input variables and the response variable. The negative estimate of riboflavin as one of the input variables indicates a direct association between riboflavin intake and T2D incidents. The micronutrient nutritional factors tryptophan and potassium represented the highest significance level in non-diabetics, considering their chi-square test results and chi-square p-value of < 0.0001.

According to the data mining analysis results in Table 3, macronutrient factors including carbohydrate, water, protein, cholesterol, saturated fatty acid (sat fat), mono unsaturated fatty acid (mono fat), and fiber had a significant association with T2D incidents (p-value < 0.05). Carbohydrates and water had a strong association with T2D development among the analyzed macronutrient nutritional factors. Our LR modeling indicated no significant association between other investigated nutritional factors and T2D.

Also, the unit odds ratios and the parameter estimate for all significant macronutrient nutritional factors were listed in Table 3. According to the achieved estimates through the LR model, protein and fiber stand for the most suitable estimates for T2D incidents (fiber estimate = 0.0084 and protein estimate = 0.009, respectively). For unit odds ratio we can interpret that, the protein variable has been identified as the most remarkable due to its high OR in the LR model. With one unit increase in protein, the chance of non-T2D development increased 1.009 times. However, represented an odd ratio lower than 1 in this evaluation (OR = 0.972), indicating that a unit decrease in mono fat is associated with a decrease in the odds of non-T2D occurrence. Prediction formula for T2D is given in Appendix.

The sign of regression coefficients (LR estimates) shows the direction of the correlation between input variables and the response variable. The negative estimate of sat fat as one of the input variables signifies a reverse association between sat fat intake and T2D incidents.

Decision tree (DT) modeling

The results of the DT for micronutrient nutritional factors are demonstrated in Fig. 1. The DT evaluated the various T2D risk factors and categorized them into 5 layers and 14 splits. In DT modeling, the first variable (root) is of the highest importance, with the following variables

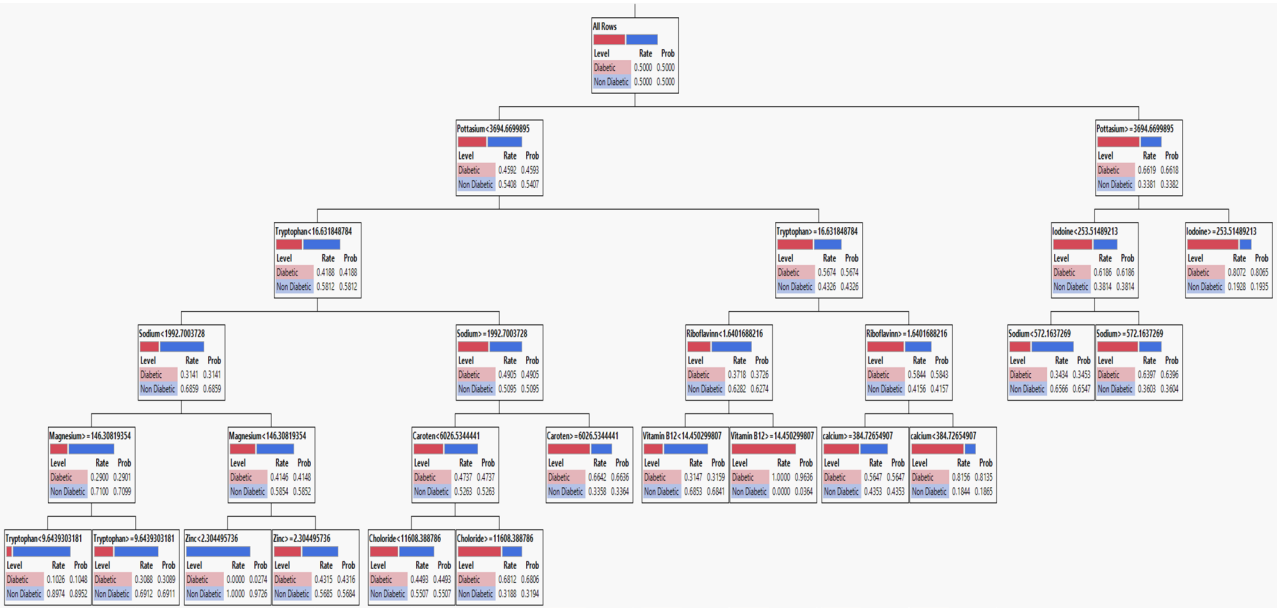

Fig. 1 DT modeling for T2D incidents based on micronutrient nutrition factors

Table 4 Rules for diabetes based on DT for micronutrient nutritional factors

Rules	Diabetic (%)	Non-Diabetic (%)
R1: Potassium < 3694.66&Tryptophan < 16.63&Sodium < 1992.70&Magnesium > = 146.30&Tryptophan < 9.64	10.48	89.52
R2: Potassium < 3694.66&Tryptophan < 16.63&Sodium < 1992.70&Magnesium > = 146.30&Tryptophan > = 9.64	30.89	69.11
R3: Potassium < 3694.66&Tryptophan < 16.63&Sodium < 1992.70&Magnesium < 146.30&Zinc < 2.30	2.74	97.26
R4: Potassium < 3694.66&Tryptophan < 16.63&Sodium < 1992.70&Magnesium < 146.30&Zinc > = 2.30	43.16	56.84
R5: Potassium < 3694.66&Tryptophan < 16.63&Sodium > = 1992.70&Caroten < 6026.53&Choloride < 11608.38	44.93	55.07
R6: Potassium < 3694.66&Tryptophan < 16.63&Sodium > = 1992.7&Caroten < 6026.53&Choloride > = 11608.38	68.06	31.94
R7: Potassium < 3694.66&Tryptophan < 16.63&Sodium > = 1992.70&Caroten > = 6026.53	66.36	33.64
R8: Potassium < 3694.66&Tryptophan > = 16.63&Riboflavinn < 1.64&Vitamin B12 < 14.45	31.59	68.41
R9: Potassium < 3694.66&Tryptophan > = 16.63&Riboflavinn < 1.64&Vitamin B12 > = 14.45	96.36	3.64
R10: Potassium < 3694.66&Tryptophan > = 16.63&Riboflavinn > = 1.64&calcium < 384.72	81.35	18.65
R11: Potassium < 3694.66&Tryptophan > = 16.63&Riboflavinn > = 1.64&calcium > = 384.72	56.47	43.53
R12: Potassium > = 3694.66&Iodine < 253.51& Sodium < 572.16	34.53	65.47
R13: Potassium > = 3694.66&Iodine < 253.51& Sodium > = 572.16	63.96	36.04
R14: Potassium > = 3694.66&Iodine > = 253.51	80.65	19.35

in the next levels of significance, accordingly [23, 25, 26]. As shown in Fig. 1, potassium has the most crucial effect on T2D development risk, followed by tryptophan, iodine, sodium, and riboflavin.

The DT indicated higher diabetes incidents among participants with higher potassium than those with lower intakes of 3694.66. In the subgroup with high potassium and high iodine, 80% of participants were diabetic. Meanwhile, among those with low potassium, low tryptophan, low sodium, low magnesium, and low zinc, 97% of subjects were identified as non-diabetic. Detailed rules for diabetes incidents created by the DT model are demonstrated in Table 4. The consequences of the DT for macronutrient nutritional factors are presented in Fig. 2. The DT estimate the various T2D risk factors and groups them into 5 layers and 11 splits. As shown in Fig. 2, protein has the most crucial effect on T2D development risk, followed by carbohydrates, cholesterol, and fiber.

The DT indicated lower diabetes incidents among participants with higher protein compared to those with lower intakes of 89.07. In the subgroup with low protein, high cholesterol, and high carbohydrate 88% of participants were non-diabetic. Meanwhile, among those with high protein and high cholesterol, 77% of subjects were identified as diabetic. Detailed rules for diabetes incidents created by the DT model are demonstrated in Table 5.

Discussion

Results from the current study indicated that among micronutrients, sodium, potassium, calcium, magnesium, zinc, iodine, carotene, vitamin D, tryptophan and

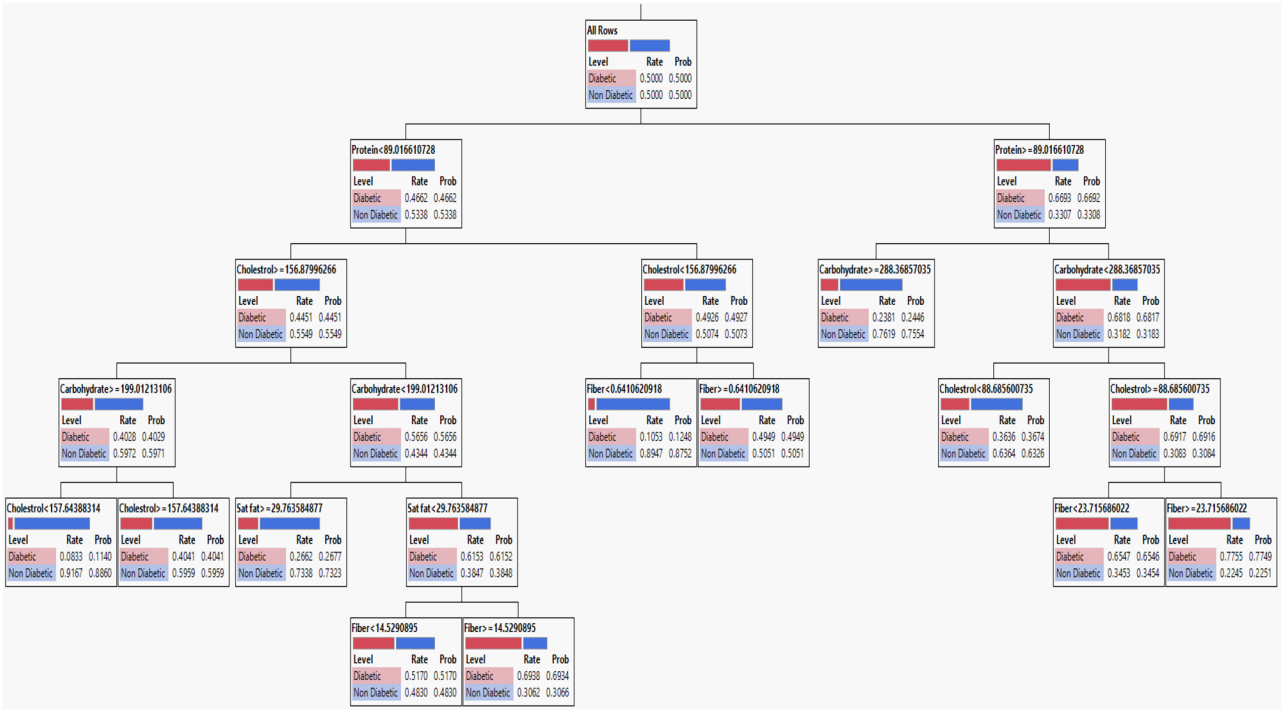

Fig. 2 DT modeling for T2D incidents based on macronutrient nutrition factors

Table 5 Rules for diabetes based on DT for macronutrient nutritional factors

Rules	Diabetic (%)	Non-Diabetic (%)
R1: Protein < 89.01&Cholestrol > = 156.87&Carbohydrate > = 199.01&Cholestrol < 157.64	11.40	88.60
R2: Protein < 89.01&Cholestrol > = 156.87&Carbohydrate > = 199.01&Cholestrol > = 157.64	40.41	59.59
R3: Protein < 89.01&Cholestrol > = 156.87&Carbohydrate < 199.01&Sat fat > = 29.76	26.77	73.23
R4: Protein < 89.01&Cholestrol > = 156.87&Carbohydrate < 199.01&Sat fat < 29.76&Fiber < 14.52	51.70	48.30
R5: Protein < 89.01&Cholestrol > = 156.87&Carbohydrate < 199.01&Sat fat < 29.76&Fiber > = 14.52	69.34	30.66
R6: Protein < 89.01&Cholestrol < 156.87&Fiber < 0.64	12.48	87.52
R7: Protein < 89.01&Cholestrol < 156.87&Fiber > = 0.64	49.49	50.51
R8: Protein > = 89.01&Carbohydrate > = 288.36	24.46	75.54
R9: Protein > = 89.01&Carbohydrate < 288.36&Cholestrol < 88.68	36.74	63.26
R10: Protein > = 89.01&Carbohydrate < 288.36&Cholestrol > = 88.68&Fiber < 23.71	65.46	34.54
R11: Protein > = 89.01&Carbohydrate < 288.36&Cholestrol > = 88.68&Fiber > = 23.71	77.49	22.51

vitamin B12 had an inverse relationship with the incidence of T2D while, phosphate, iron, chloride, and riboflavin intake were positively associated with the risk of diabetes. In the macronutrient group, water, protein, and fiber intake had a protective effect against the incidence of diabetes while carbohydrate saturated fat, mono fat, and cholesterol had a positive correlation with the incidence of T2D. It seems that the increasing prevalence of type 2 diabetes is due to increased obesity, decreased physical activity, and dietary changes. Many observational studies have shown that macronutrient (protein, carbohydrate, fiber, and fat) and micronutrient (vitamins and minerals) intake are associated with the incidence of diabetes [27–30].

Micronutrient nutritional intake factors

Our DT model indicated that potassium, tryptophan, iodine, sodium, and riboflavin intake had the most significant effect on the incidence of diabetes, respectively. In the subgroup with higher potassium, lower iodine, higher magnesium, and lower tryptophan intake, the risk of diabetes was approximately 98%. According to our results, in the subgroup with lower potassium intake, lower tryptophan intake, and lower sodium intake, the incidence percentage of diabetes for both subgroups of higher magnesium and lower magnesium and lower zinc intake was 96%.

Magnesium deficiency plays a key role in the pathogenesis of diabetes [31]. Lower magnesium levels can inactivate cellular defenses against oxidative stress effects [32]. It was also shown that In over 300 enzymatic reactions,

magnesium is a necessary cofactor, specifically in all phosphorylation reactions and in general in all reactions involving the utilization and transfer of ATP, such as cellular responses to growth factors and cell proliferation [33, 34]. Through its role as an enzyme cofactor, magnesium may directly influence glucose metabolism in cells [35, 36] and may interact with calcium homeostasis to influence insulin secretion [37]. In the present study, magnesium intake was higher in T2D patients, which correlates with other research results [38, 39]. We also found that magnesium intake had an inverse association with the incidence of diabetes, which is consistent with previous investigations [39, 40].

We found that thiamin, vitamin C, vitamin D, riboflavin, folate, and niacin levels were higher in the T2D group while there were no significant differences in vitamin B12 intake between the case and control group. Furthermore, vitamin B12 and vitamin D intake had an inverse correlation with T2D incidence, while riboflavin had a positive association with the incidence of T2D. There was no significant association between thiamin, vitamin C, folate, and niacin intake with T2D incidence. Walter et al. [41] demonstrated that thiamin was higher in diabetic patients, while there were no significant differences between vitamin C, vitamin B12, and vitamin D between cases and controls. In contrast to our results, it was shown that thiamin had lower levels in diabetics [42]. This inconsistency may be due to multi-vitamin consumption or differences in sample size. A cohort study has shown a positive relationship between riboflavin intake and the prevalence of diabetes [43]. Our results are consistent with previous studies which found that there is an inverse correlation between vitamin D levels and the incidence of diabetes [44, 45]. However, in a few studies, there was no significant association between vitamin D intake and the incidence of diabetes [17]. Some studies found that serum vitamin B12 had no significant differences between T2D patients and nondiabetics in agreement with our results [46].

The results of this study indicated that phosphate and calcium levels were higher in the case group. These results agree with previous studies [47]. However, a few studies demonstrated that levels of phosphate and calcium were lower in the T2D group [48]. Furthermore, we indicated that there is an inverse correlation between calcium intake and the incidence of diabetes, while this association was positive between serum phosphate and the risk of diabetes.

This study supports evidence from previous investigations [16, 49].

We indicated that iron intake has a positive association with the occurrence of diabetes. This result reflects those of a prospective cohort study which also found a positive correlation between iron intake and the incidence of T2D in women [50]. However, another prospective cohort study between the men population indicated no significant association between total iron intake and the incidence of diabetes but a positive correlation between Heme-iron intake from red meat and the risk of diabetes [51].

Zinc deficiency is related to increased oxidative stress and many clinical complications, such as impaired wound healing and taste acuity in diabetic patients [52]. We indicated that zinc intake was higher in T2D patients. We also showed that there is an inverse relationship between zinc intake and the incidence of diabetes. These results are in line with those of previous studies [53, 54]. However, a study in the United States doesn't support the thesis that zinc status is inversely associated with the incidence of diabetes [55]. There may be a few explanations for this finding: (1) the mean age for this study was 27.03 which is lower than the mean age of our study (52.18); (2) average zinc intake was higher (16.7 mg/day) in comparison to our study (9.77 mg/day).

There are few studies about the relationship between iodine intake and the incidence of diabetes. A cohort study has shown a positive correlation between iodine intake and the incidence of diabetes [56]. However, the current study findings do not support the previous research. We indicated an inverse relationship between iodine intake and the incidence of diabetes. A possible explanation for this might be that only women were investigated in this study. Another possible explanation for this is that the average iodine intake (155.6 μg/day) was higher than our study (108.18 μg/day). However, further work is required to investigate the relationship between dietary iodine intake and the incidence of diabetes. We found that tryptophan had a protective effect against the incidence of diabetes. This result was in accord with a recent study showing that dietary tryptophan was associated with decreased risk of T2D [57]. However, a few studies do not support our results [58].

We demonstrated that potassium intake had an inverse correlation with the risk of diabetes. This result is in agreement with previous studies [59]. Cardiovascular disease (CVD) risk is higher in T2D patients [60]. It was shown that higher sodium intake was associated with hypertension and an increased risk of CVD [61, 62]. Iran had one of the highest salt intakes worldwide at 9.52 g/day [63]. The current study indicated that sodium intake was higher in T2D patients. Furthermore, there was no significant association between sodium intake and the development of diabetes. These results are consistent with previous studies [64]. We found that chloride intake had a positive relationship with the incidence of T2D. Some studies have shown that there is a positive correlation between salt intake and the incidence of diabetes [65]. While some studies indicated that lower dietary salt

intake was associated with an increased risk of diabetes [66]. Further research should be undertaken to investigate the association between salt intake and the incidence of diabetes.

Macronutrient nutritional intake factors

According to our DT algorithm, protein, carbohydrate, cholesterol, and fiber intake had the most crucial effect on the risk of T2D, respectively. We indicated that in the subgroup with higher protein and carbohydrate intake the risk of diabetes development was 94%. In the subgroup with lower protein, lower cholesterol, lower carbohydrate, lower saturated fat, and lower fiber intake, the incidence of diabetes was 86%.

In this study, water intake was higher in T2D patients than in the control group. We also indicated that water intake had a protective effect against T2D incidence. These results are consistent with a recent study showing an inverse relationship between water intake and the incidence of diabetes among men and women [67]. The hyperglycemia produce the symptoms of repeated urination, increased thirst, and increased hunger [68]. Also, we found that carbohydrate intake was higher in T2D patients. Another result was that carbohydrate intake positively affected the incidence of diabetes. These results agree with previous studies [28]. Another result of our study was a small inverse relationship between fiber and protein intake and the incidence of diabetes. These results support other studies [38, 69]. However, A cohort study of the European population indicated that high protein intake was associated with a small elevated risk of T2D [66, 70]. It seems possible that this inconsistency may be due to differences in dietary habits and animal protein consumption or plant protein intake.

We demonstrated that cholesterol intake had no significant differences between the case and control groups. Furthermore, we indicated that there is a positive correlation between dietary cholesterol intake and the incidence of diabetes. A prospective cohort study of French women showed the same result as our result [71].

To our knowledge, this is the largest study so far documenting the correlation between micro/macro nutrients and the incidence of diabetes. Another strength of our study was that it has been one of the first studies using the Gini impurity index to construct a DT machine learning model to indicate the correlation between nutrient factors and the incidence of T2D. Furthermore, the sample size and long follow-up duration might be considered the strengths of our study. We also used analysis models (LR and DT) to evaluate the association between nutrient factors and the risk of diabetes more accurately.

This study was limited by the absence of adjusting the incidence estimates by smoking, drug use, body mass index (BMI), family history of diabetes, and sex that may influence the result. More research using control trials is needed to evaluate the effect of micro/macro nutrients on diabetes, especially in iodine and sodium intake.

Conclusion

We indicated that nutritional intake of potassium, calcium, magnesium, zinc, iodine, carotene, vitamin D, tryptophan, and vitamin B12 had an inverse correlation with the incidence of diabetes while phosphate, iron, chloride, and riboflavin had a positive relationship with the risk of T2D. We found that water, protein, and fiber intake had a protective effect against T2D incidence among macronutrients. However, dietary carbohydrate and cholesterol intake had a positive correlation with the occurrence of diabetes.

Appendix

A. **Formula for predicting T2D occurrence by micronutrients**.

By applying the results obtained in Table 2, the regression formula for predicting diabetes based on significant factors is as follows:

$$P\left(Diabetes\right) = \frac{exp\left(f\right)}{1 + exp\left(f\right)},$$

where f is obtained from Table 2 as:

$$\begin{aligned} f = {} & 0.00062836\ (\text{sodium}) + 0.00043418\ (\text{potassium}) \\ & + 0.00066181\ (\text{calcium}) + 0.00160418\ (\text{magnesium}) \\ & - \ 0.0016375\ (\text{phosphate}) - 0.0368858\,(\text{iron}) \\ & + 0.04180353\ (\text{zinc}) - \ 0.0004067\ (\text{chloride}) \\ & + 0.00242454\ (\text{iodine}) + 6.59415\text{e} - 5\ (\text{carotene}) \\ & + \ 0.03232205\ (\text{vitamin D}) - 0.3540253\,(\text{riboflavin}) \\ & + \ 0.10183327\ (\text{tryptophan}) + 0.03114934\ (\text{vitamin b12}) \\ & - 1.8237199 \end{aligned}$$

For example, for an individual with the following characteristics, we get $P\left(Diabetes\right) = \ 0.4781$ indicating that getting diabetes is 0.4781.

$$\begin{aligned} & sodium = 1673.55,\ \ potassium = 2708.52, \\ & calcium = 1275.18,\ \ magnesium = 196.17, \\ & phosphate = 1836.69,\ \ iron = 5.20, \\ & zinc = 11.68,\ \ chloride = 1748.86, \\ & iodine = 327.35,\ \ carotene = 405.21, \\ & vitamin\ D = 2.38,\ \ riboflavin = 2.61, \\ & tryptophan = 18.46,\ \ vitamin\ b12 = \ 3.03. \end{aligned}$$

B. **Formula for predicting T2D occurrence by macronutrients**.

By applying the results obtained in Table 3, the regression formula for predicting diabetes based on significant factors is as follows:

$$P\left(Diabetes\right) = \frac{exp\left(f\right)}{1 + exp\left(f\right)},$$

where f is obtained from Table 3 as:

$$\begin{aligned} f = {} & 0.00037506\ \left(Water\right) + 0.00985559\ \left(Protein\right) \\ & - 0.0118932\ \left(Carbohydrate\right) + 0.00840613\ \left(Fiber\right) \\ & - 0.0243156\ \left(Sat\ fat\right) - 0.0274008\ \left(Mono\ fat\right) \\ & - 0.0008959\ \left(Cholesterol\right) + 2.48497054 \end{aligned}$$

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Author contributions
A.M., M.R., E.D., and H.E. contributed to the conception and design of the study. M.M. and D.T. collected the data and F.S. and M.A. performed data analysis. M.M. and S.G. and A.R. drafted and M.G. and G. F. edited the manuscript. All the authors approved the final version of the manuscript.

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Data availability
The manuscript contains third party material and obtained permissions are available on request by the Publisher.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences (MUMS).

Consent for publication
The manuscript was approved by all authors for publication.

Competing interests
The authors declare that they have no competing interests.

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