Causal association pathways between fetuin-A and kidney function: A mediation Analysis

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Abstract

Background

Body mass index (BMI), uric acid (UA) diabetes mellitus (DM) and hypertension (HT) are known risk factors of declined kidney function, and are associated with fetuin-A. However, the causal pathways of these associations are unclear. We therefore used cohort data to explore possible causal pathways of fetuin-A and kidney function.

Methodology

We used data of the Electricity Generating Authority of Thailand cohort 2009 (n= 2305). A causal pathway was constructed, which considered fetuin-A as study factor, BMI, UA, DM, and HT as mediators, and eGFR as the outcome. A generalized-structural equation model (GSEM) with 1000-replication bootstrapping was applied to assess the causal effects adjusting for covariates.

Results

The fetuin-A → eGFR pathway showed a direct association of fetuin-A on eGFR with the coefficient of -0.0072 (95% CI: -0.0119, -0.0025). In addition, the indirect effects of fetuin-A→ BMI → eGFR was also significant with the coefficient of 0.00086 (0.00025, 0.0016; implying that every one unit of BMI increased, resulting from increasing fetuin-A, would significantly increase eGFR 0.00086 (0.00025, 0.0016) mL/min/1.73m^2. There was a negative effect of fetuin-A on eGFR through BMI and UA pathway (Fetuin-A→BMI→UA→eGFR) as well as the HT pathway (Fetuin-A→BMI→HT→eGFR) with average casual mediation effects (ACME) of -0.00132 (-0.00177, -0.00092) and -0.00139 (-0.00237, -0.00069). Fetuin-AàDMàHTàeGFR was also statistically significant with the ACME of -0.00223 (-0.00535, -0.00066).

Conclusion

Our study has shed some light on the possible role of fetuin-A in the etiology of declining renal function through the mediatory roles of BMI, UA, DM and HT in the various complex causal pathways leading to declining kidney function in our study cohort. Further studies are however recommended to examine the pathomechanisms involved in the mediational processes of these studied risk factors in the etiology of declining kidney function.

Background

Chronic kidney disease (CKD) is a global public health problem with rising numbers of renal failure(1, 2). The report of the 2015 Global Burden of Disease Study indicated that kidney disease was the 12th most common cause of death, which accounted for 1.1 million deaths worldwide(1). Known risk factors for declined kidney function have been reported including body mass index (BMI)(3, 4), uric acid (UA)(5, 6), diabetes mellitus (DM)(7–9) and hypertension (HT)(10, 11). Some evidences have also shown that inflammatory markers (e.g., high sensitivity C-Reactive protein (hsCRP), interleukin-1 (IL-1), endothelin-1 (ET -1), and tumor necrosis factor-α (TNF-α)(12, 13)) are associated with eGFR decline. In addition, recent evidences from observational studies showed that fetuin-A was also associated with CKD morbidity(14, 15) and mortality(16, 17). Moreover, fetuin-A has been found to be associated with CKD risk including BMI(18), DM(19, 20) and HT(21, 22). However, the causal pathways of these disease phenotypes are quite complex and not fully understood. Fetuin-A might be directly associated with declined eGFR, or it might affect eGFR through mediators (i.e., BMI, UA, DM, and HT) which are also individually associated with declining eGFR.

Considering the fact that fetuin-A, a pleiotropic multi-functional circulating glycoprotein, had been found to be associated with the afore-mentioned disease phenotypes, we therefore conducted a study using data from a prospective cohort of the Electricity Generating Authority of Thailand (EGAT) to explore the causal association pathways of these diseases with fetuin-A in relation to declining kidney function.

Design

We used cross-sectional data of EGAT prospective cohort(23), who were recruited in 2009 and followed up in 2014 (5 years later) with a sample sizes of 2,564. The cohort was originally designed to assess risk factors for cardiovascular diseases, psychological distress, health status, functional status and health-related quality of life. All EGAT's employees aged 18 years or older were invited to voluntarily participate in this cohort study after obtaining their written informed consent. At inception, the subjects underwent medical examinations including laboratory tests and also completed a self-administered questionnaire on their lifestyle behavior and family history of disease. Members of the respective cohorts are resurveyed regularly every 5 years.

The main study factor was serum fetuin-A, which was measured using specimens that were collected at the baseline survey in 2009 by sandwich enzyme immunoassay (R&D Systems, Inc., Minneapolis, MN, USA). Precisions of intra- and inter-assays were 4.9% and 7.3%, respectively(18). Our interested clinical outcome was estimated eGFR which was estimated based on the CKD-EPI Creatinine Eq. (2009)(24) using serum creatinine, age and sex parameters. In addition, we also had intermediate outcomes, which were considered as mediators, including BMI, UA, DM, and HT. The outcome and mediators were measured at survey 2009 and 2014. BMI was calculated as weight (kg)/height (m^2). UA was assessed by the spectrophotometric absorption technique after treatment of the specimen with the enzyme uricase. Then, it was classified as normal if the value was in the range 2.5 to 7.5 milligrams /deciliter (mg/dL) for women and 4.0 to 8.5 mg/d for men(25), otherwise it was abnormal. DM was diagnosed if fasting blood sugar (FBS) was ≥ 7.0 mmol/l (or 126 mg/dl) with/without a history or evidence of use of anti-diabetic medication(26). Subjects were classified as HT if they took any of antihypertensive drugs (e.g., calcium channel blockers, beta-blocker, angiotensin converting enzyme (ace) inhibitors, and etc.), or had systolic blood pressure (SBP) or diastolic blood pressure (DBP) ≥ 140 and ≥ 90 mmHg, respectively. Blood pressure was measured twice; taken 5 minutes apart and allowing for a 5-minutes rest after the first measurement. Covariables that were considered included demographic variables (i.e., age, gender), smoking history (current/ex-smokers and non-smokers), alcohol consumption (current/ex-drinkers and non-drinker), triglyceride, and LDL.

Statistical analysis

Baseline and follow-up demographic variables were analyzed and reported as means ± SD for continuous data, frequency and percentage for categorical data. Multiple mediation analysis was performed according to the causal association pathways (See Fig. 1. Causal association pathways between fetuin-A and eGFR), in which fetuin-A was considered as independent variable, BMI, UA, DM, and HT were mediators, and eGFR was the outcome. All possible serial multiple mediation models were constructed, see Supplement Table 1. Mediation and outcome models were constructed by fitting fetuin-A on each of the four mediators (i.e., BMI, UA, DM, and HT) using generalized linear structural equation models (GSEM) with logit link for DM and HT, and identity link for BMI, UA, and eGFR.

Table 1
Baseline Characteristics of study subjects

Characteristics	Survey 2009	Survey 2014
Number of subjects	2564	2305
Age, year, mean (SD)	41 ±7	46 ±7
Gender, number (%)		
Male	1882 (73.4)	1656 (71.8)
Female	682 (26.6)	649 (28.2)
Marital Status, number (%)		
Single	745 (29.1)	461 (20.0)
Married	1705 (66.5)	1641 (71.2)
Divorced/Widowed	114 (4.4)	203 (8.8)
Income, Baht/month, number (%)		
<20,000	130 (5.1)	-
20,000–49,999	970 (38.1)	-
≥50,000	1446 (56.8)	-
Education, number (%)		
≤Secondary school	115 (4.5)	75 (3.3)
Vocational	584 (22.8)	473 (20.5)
≥Bachelor	1865 (72.7)	1757 (76.2)
Smoking, number (%)		
Never smoker	1683 (65.7)	1499 (65.0)
Ex-smoker	450 (17.6)	475 (20.6)
Current smoker	428 (16.7)	331 (14.4)
Alcohol, number (%)		
Never Drinkers	981(39.1)	906 (39.3)
Quit drinkers	171(6.8)	-
Current drinkers	1358 (54.1)	1399 (60.7)
Exercise, times/week, number (%)		
None	1503 (58.7)	743 (32.2)
1–2	406 (15.8)	446 (19.4)
≥3	652 (25.5)	1116 (48.4)
Diabetes		

Characteristics	Survey 2009	Survey 2014
Yes	117 (4.6)	236 (10.2)
No	2440 (95.4)	2069 (89.8)
Hypertension		
Yes	500 (22.6)	809 (35.1)
No	1984 (77.4)	1496 (64.9)
BMI, kg/m^2, mean (SD)	24.0 ±3.7	24.8 ±3.8
Fetuin, mg/dl, mean (SD)	558.9 ±110.5	-
Uric Acid, mg/dl, mean (SD)	5.6 ±1.5	5.8 ±1.5
Cholesterol, mg/dl, mean (SD)	216.8 ±39.3	217.4 ±40.3
HDL, mg/dl, mean (SD)	51.7 ±12.3	58.3 ±15.5
LDL, mg/dl, mean (SD)	148.4 ±36.9	148.6 ±37.7
Triglyceride, mg/dl, mean (SD)	129.1 ±90	131.8 ±84.1
eGFR, ml/min/1.73 m^2, mean (SD)	98.7 ±23.6	92.4 ±22.9

A univariate GSEM model was used to screen the covariables (i.e., age, gender, smoking, alcohol, triglycerides, and LDL) that might associate with each of mediators (i.e., BMI, UA, DM, and HT). Forward selection was applied to select significant variables in the mediation and outcome models that already contained fetuin-A. Mediated effects were then estimated by product coefficients of each pathway, see Supplement Table 1. Finally, bias corrected bootstrap with 1000 replications was used to estimate average mediation effects(27). All analyses were performed using STATA(28) version 15, p- value of < 0.05 was considered statistically significant.

Results

Baseline characteristics are described (see Table 1), in which 2564 subjects were enrolled in 2009 but only 2305 subjects remained for follow up in the 2014 survey. Mean age, BMI, UA, and eGFR at baseline were respectively 46 ±7 years, 24.8 ±3.8 kg/m^2, 5.6 ±1.5, and 98.7 ±23.6, whereas the prevalence of DM and HT were 4.6% and 22.6%.

The univariate GSEM showed that fetuin-A significantly associated with all mediators (BMI, UA, DM, and HT) and eGFR outcome see Supplement Table 2. In addition, all covariables including age, sex, smoking, alcohol, triglyceride, and LDL were also significantly associated with each mediator and eGFR. Multivariate GSEMs were then constructed considering all 6 covariables for BMI, UA, DM, and HT and eGFR models, see Table 2. After adjusting covariables, fetuin-A was significantly associated with only mediator BMI and DM but not with UA and HT. In addition, fetuin-A was also significantly associated with eGFR.

Table 2
Causal associations between fetuin-A and eGFR: Multivariate GSEM models

Equation	Factors	b	SE	z	p	95%CI
Fetuin-A→ BMI	Fetuin	0.0039	0.0006	7.12	< 0.001	0.0029, 0.0051
	Age	0.0368	0.0088	4.17	< 0.001	0.0195, 0.0541
	Male vs. Female	1.4058	0.1549	9.08	< 0.001	1.1022, 1.7093
	Smoking					
	Ex-smoker	0.4306	0.1718	2.51	0.012	0.0939, 0.7674
	Current smoker	-0.3115	0.1890	-1.65	0.099	-0.6820, 0.0589
	Alcohol drinking					
	Ex-drinker	0.5371	0.2417	2.22	0.026	0.0634, 1.0108
	Current drinker	0.3329	0.1463	2.28	0.023	0.0463, 0.6196
	Triglyceride	0.0109	0.0008	14.19	< 0.001	0.0094, 0.0124
	LDL	0.0062	0.0017	3.66	< 0.001	0.0029, 0.0096
Fetuin-A→Uric acid	Fetuin	0.0002	0.0002	1.29	0.196	-0.0001, 0.0006
	BMI	0.0849	0.0055	15.51	< 0.001	0.0742, 0.0957
	Male vs. Female	1.5952	0.0493	32.33	< 0.001	1.4984, 1.6919
	Smoking					
	Ex-smoker	-0.0095	0.0543	-0.17	0.862	-0.1159, 0.0969
	Current smoker	-0.1707	0.0597	-2.86	0.004	-0.2877, -0.0537
	Alcohol drinking					
	Ex-drinker	0.0859	0.0764	1.13	0.261	-0.0638, 0.2356
	Current drinker	0.2249	0.0462	4.87	< 0.001	0.1343, 0.3155
	Triglyceride	0.0025	0.0002	10.19	< 0.001	0.0020, 0.0030

Equation	Factors	b	SE	z	p	95%CI
Fetuin-A→DM	Fetuin	0.0015	0.0005	2.75	0.006	0.0004, 0.0026
	BMI	0.1870	0.0159	11.71	< 0.001	0.1557, 0.2183
	Uric acid	-0.2350	0.0527	-4.46	< 0.001	-0.3383, -0.1317
	Age	0.0639	0.0092	6.96	< 0.001	0.0459, 0.0820
	Male vs. Female	0.5310	0.1725	3.08	0.002	0.1930, 0.8690
	Triglyceride	-0.0102	0.0017	-5.86	< 0.001	-0.0136, -0.0068
	LDL	0.0025	0.0006	4.03	< 0.001	0.0013, 0.0037
Fetuin-A→HT	Fetuin	0.0008	0.0004	1.89	0.059	-0.00003, 0.0016
	BMI	0.1389	0.0132	10.54	< 0.001	0.1131, 0.1647
	Uric acid	0.1759	0.03333	5.28	< 0.001	0.1106, 0.2413
	DM	0.5955	0.1338	4.45	< 0.001	0.3333, 0.8576
	Age	0.0919	0.0069	13.39	< 0.001	0.0784, 0.1053
	Triglyceride	-0.0066	0.0013	-5.28	< 0.001	-0.0091, -0.0042
	LDL	0.0031	0.0005	5.71	< 0.001	0.0020, 0.0042
Fetuin→BMI→UA→ DM→HT→ eGFR	Fetuin	-0.0077	0.0022	-3.49	< 0.001	-0.0119, -0.0034
	BMI	0.1889	0.0724	2.61	0.009	0.0471, 0.3308
	Uric acid	-3.9997	0.1866	-21.43	< 0.001	-4.3655, -3.6339
	DM	-0.3346	0.8087	-0.41	0.679	-1.9196, 1.2503
	HT	-2.6717	0.5706	-4.68	< 0.001	-3.7901, -1.5534
	Alcohol drinking					
	Ex-drinker	-5.1275	0.9180	-5.59	< 0.001	-6.9268, -3.3283

Equation	Factors	b	SE	z	p	95%CI
	Current drinker	-1.2136	0.5342	-2.27	0.023	-2.2606, -0.1665
	Triglyceride	0.0077	0.0031	2.50	0.012	0.0017, 0.0138

A bootstrap with 1000-replication was applied to estimate average causal mediation effects (ACMEs), see Table 3. The result indicated that most fetuin-A effects on eGFR through BMI pathway were significant. For instance, ACME of Fetuin→BMI→eGFR pathway was 0.000864 (0.00025, 0.00163), i.e., increasing fetuin-A one unit would increase BMI and then increased eGFR of 0.000864 unit. Fetuin-A effects through BMI and then UA pathway (Fetuin→A→BMI→UA→eGFR) and HT pathway (Fetuin-A→BMI→HT→eGFR) showed significantly negative effects, i.e., lowering eGFR with ACMEs of -0.00132 (-0.00177, -0.00092) and − 0.00139 (-0.00237, -0.00069). In addition, fetuin-A◊DM◊HT◊eGFR was also statistically significant with the ACME of -0.00223 (-0.00535, -0.00066). None of the other three single-mediator pathways: fetuin-A◊UA, fetuin-A◊DM, and fetuin-A◊HT, was statistically significant.

Table 3
Estimation of average causal mediation effects using bootstrapping

Paths	Effect	SE	Z	P-value	95% CI
Fetuin→eGFR (direct effect)	-0.00721	0.00260	-2.77	0.006	-0.01190, -0.00247
BMI-mediator					
Fetuin→BMI→eGFR	0.000864	0.000353	2.45	0.014	0.00025, 0.00163
Fetuin-A→BMI→UA→eGFR	-0.00132	0.00022	-5.99	<0.001	-0.00177, -0.00092
Fetuin-A→BMI→DM→eGFR	-0.000165	0.000674	-0.24	0.807	-0.00149, 0.00116
Fetuin-A→BMI→HT→eGFR	-0.00139	0.000416	-3.35	0.001	-0.00237, -0.00069
Fetuin-A→BMI→UA→DM→eGFR	0.000018	0.000076	0.23	0.817	-0.00005, 0.00028
Fetuin-A→BMI→UA→HT→eGFR	-0.00015	0.000054	-2.77	0006	-0.00028,-0.00007
Fetuin-A→BMI→UA→DM→HT→eGFR	0.000119	0.000055	2.16	0.031	0.00005, 0.00028
UA mediator					
Fetuin→ UA→eGFR	-0.00089	0.00067	-1.35	0.177	-0.00216, 0.00039
Fetuin→UA→DM→eGFR	0.00001	0.00007	0.17	0.863	-0.00006, 0.00024
Fetuin→UA→HT→eGFR	-0.00010	0.00009	-1.18	0.237	-0.00031, 0.00003
Fetuin→UA→DM→HT→eGFR	0.00008	0.00007	1.11	0.269	-0.00002, 0.00032
DM mediator					
Fetuin→ DM→eGFR	-0.00033	0.00139	-0.24	0.812	-0.00332, 0.00230
Fetuin→ DM→HT→eGFR	-0.00223	0.00113	-1.97	0.049	-0.00535,-0.00066
HT mediator					
Fetuin-A→ HT→eGFR	-0.00192	0.00118	-1.64	0.102	-0.00459, 0.00008

Discussion

We had explored causal pathway of fetuin-A and kidney function through BMI, UA, DM, and HT using multiple mediation analysis. Our findings indicated that fetuin-A directly associated with decreasing eGFR. In addition, effects of fetuin-A on eGFR was found to pass through the following mediators: BMI, UA (fetuin-A→BMI→UA→eGFR) and HT (fetuin-A→BMI→HT→eGFR), i.e., every unit of fetuin-A increased would increase BMI and UA risk resulting in a decrease in eGFR of 0.00132 ml/min/1.73 m^2. Likewise, increasing fetuin-A would increase BMI, HT risk, and decrease eGFR by 0.00139 ml/min/1.73 m^2. Furthermore, effects of fetuin-A could be mediated through DM and HT resulting in the lowering of eGFR.

Our finding with regards to the association of fetuin-A level with eGFR is similar to a previous study by Ix et al(29), which showed negative association between fetuin-A and predominantly non-diabetic subjects with stage 3 or 4 CKD, i.e., high fetuin-A level and low eGFR. Contrastingly, previous observational studies(14, 15, 30) found positive association between fetuin-A and kidney function, i.e., decreasing serum fetuin-A would decrease eGFR. It is worth noting that the functions and regulatory mechanisms of fetuin-A are complex, and may seem to differ according to the pathophysiologic characteristics of the population being studied(14). Several studies have demonstrated that inflammatory processes are increased in CKD, even in the early stages of CKD, and that the inflammatory processes triggered by inflammatory markers such as CRP and adiponectin are linked to endothelial dysfunction(14, 31, 32)

Fetuin-A, an anti-inflammatory protein acts as a negative acute phase reactant in the extra-cellular space to attenuate inflammatory responses, as such in patients with less advanced stages of CKD, and likely in the early phase of inflammation, fetuin-A levels may be normal or raised, however its expression is negatively regulated by pro-inflammatory cytokines such as CRP, which downregulates its synthesis during inflammation.(33, 34) Therefore, in a sustained inflammatory response, circulating fetuin-A levels are progressively depleted and its protective role in halting further decline of kidney function is undermined. Moreover, though not consistently demonstrated(16), variations in fetuin-A levels may also be determined by genetic polymorphisms independent of inflammation(15, 35).

Overweight/ obesity are known risk factors of cardiovascular disease (CVD)(36) and declining kidney function(4, 37). In addition, overweight/obesity is also highly associated with other CVD risks such as UA(38), DM(39) and HT (40), which may impact on kidney function as demonstrated by our findings. However, our mediation analysis showed positive causal effect of fetuin-A on eGFR that was mediated through BMI, i.e., BMI was a protective factor on kidney function. This might imply that the kidney function of subjects with high BMI could still be in good condition, if there are no associated risk factors such as hyperuricemia, DM, and HT.

Diabetes and hypertension are comorbid conditions frequently associated with kidney functions(41, 42). The role of DM in the pathogenesis of kidney disease has been established by epidemiological studies(9). Older subjects with longer duration of DM have a higher risk of developing CKD(43) and about 40% of patients with DM develop impaired kidney function, albuminuria, or both(44). Common kidney diseases which are associated with DM include CKD, ischemic nephropathy related to diabetic vascular disease and hypertensive nephrosclerosis(45, 46)

Fetuin-A is secreted predominantly by the hepatocytes and is encoded by the alpha Heremans-Schmidt glycoprotein (AHSG) gene, which is located on chromosome (3q27)(47). Its physiologic role includes the regulation of bone metabolism and the inhibition of vascular calcification. It has been implicated in vascular inflammatory processes as well as in the etiology of complex diseases such as CVDs(48) and DM(19, 20). Though some studies have been conducted to assess the relation of fetuin-A to CKD morbidity and progression (14, 49), and mortality(30, 33, 50) however its role in the etiology of kidney disease remains unclear.

Some observational studies have shown that increasing fetuin-A levels is associated with both improvements in the CKD status(31, 33) and endothelial dysfunction (ED)(31). ED is considered to be one of the major causal pathomechanisms of CKD(14, 51). Additionally, ED has equally been implicated in the pathophysiology of different forms of complex phenotypes like hypertension / coronary artery disease(52), DM(53) and CKD(54), which might be associated with the ED vascular inflammatory processes.

Out study have some strength. We assessed not only the direct causal effect of fetuin-A on kidney function but also the effects that were mediated through known risk factors of kidney function including BMI, UA, DM, and HT. We applied a multiple-mediation analysis model to determine possible causal pathways and effects of fetuin-A on eGFR. We used the EGAT prospective cohort to demonstrate the causal pathways that fetuin-A could have on kidney function through multiple mediator pathways, adjusting for covariables, which were obtained during the baseline and follow-up visits. A few limitations should however be addressed. Although we used longitudinal data from the EGAT cohort, fetuin-A was measured only once at baseline because of budget limitation. We considered intermediate mediators and also surrogate outcome of eGFR instead off end-clinical outcomes because the cohort had been followed up for only 5 years.

In conclusion, fetuin-A might have direct effect on declining kidney function, in which increasing fetuin-A might reduce kidney function. In addition, its effects might be mediated through multiple mediators including BMI, UA, DM, and HT, resulting in the lowering of eGFR. High level fetuin-A might increase BMI, however among this EGAT cohort that were studied, raised BMI on its own had no effect on declining kidney. The effect of raised BMI in declining kidney function was observed with the inclusion of other risk factors such as DM, HT, or high UA. These findings would however need to be further assessed in a cohort with a longer follow-up period.

Abbreviations

AHSG alpha Heremans-Schmidt glycoprotein

BMI body mass index

CKD chronic kidney disease

CVD cardio vascular disease

DBP diastolic blood pressure

DM diabetes mellitus

EGAT Electricity Generating Authority of Thailand

eGFR estimated glomerular filtration rate

ET endothelin

GSEM generalized-structural equation model

hsCRP high sensitivity C-Reactive Protein

HT hypertension

IL Interleukin

SBP systolic blood pressure

TNF tumor necrosis factor

UA uric acid

Declarations

Ethics approval and consent to participate

The ethical approval of the EGAT cohort study was given by Faculty of Medicine Ramathibodi Hospital, Mahidol University.

Duly signed consent was obtained from all the subjects before they were recruited into the study after the benefits and possible harms of the study was explained to them. The anonymity of the subjects was also ensured

Consent for publication

Not applicable.

Availability of data and materials

a. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All the authors declare that they have no competing interests in this study

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None.

Authors' contributions

The data analysis was carried out by PEM and AT. The initial draft of the manuscript was done by PEMB while the proof-reading was done by AT, PN, PS and MM. Data validation and reference check was done by SR and PN. All authors read and approved the final manuscript."

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Figures

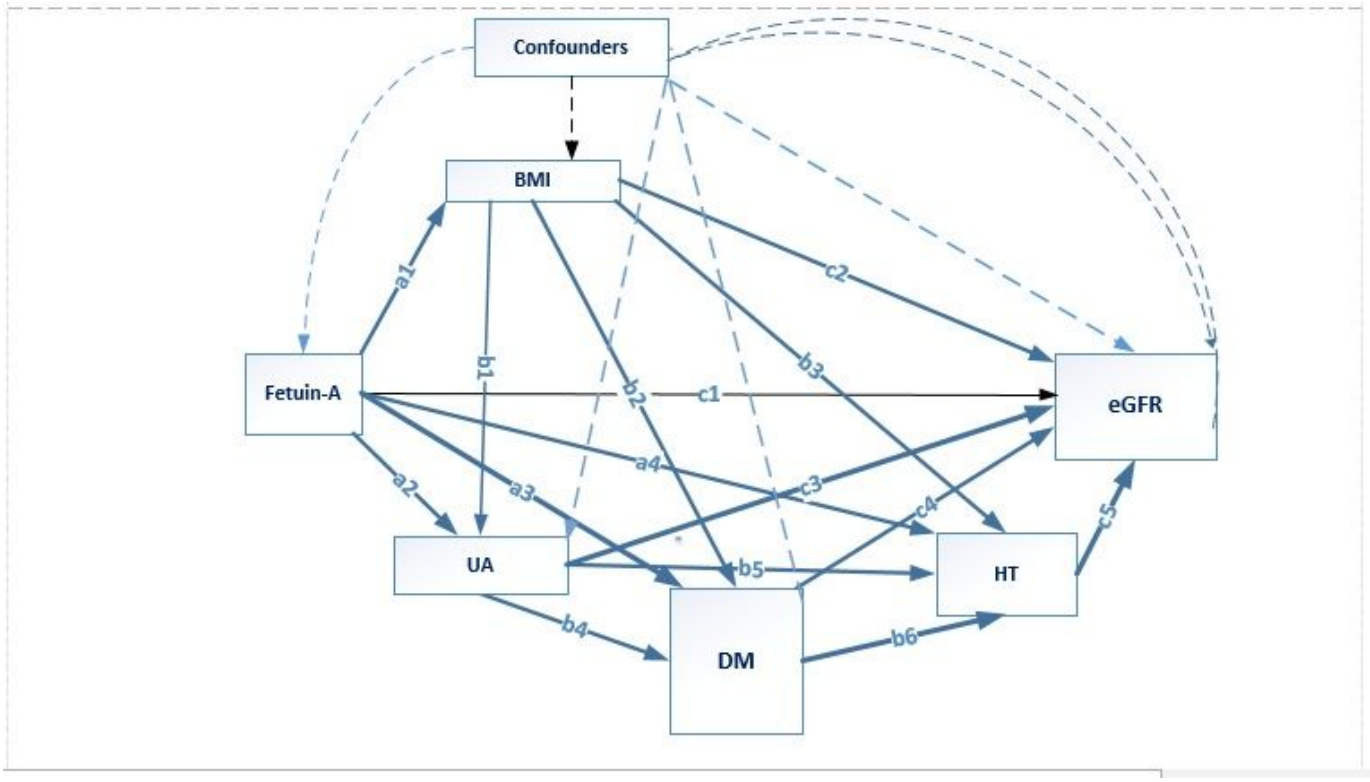

Figure 1

Causal association pathways between fetuin-A and eGFR

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