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Biochemical study of apelin hormone and its relationship to insulin and insulin resistance in the serum of obese patients in Nineveh Governorate

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***Abstract*---**The research included (117) cases collected from AL Salam Teaching Hospital in Mosul city, the cases were divided into two group, the first group included (93) patients with obesity either the second group included (24) healthy cases, both groups were divided into three subgroups: (20-35) (36-50) (51 and over) year, and included estimation of Apelin hormone, insulin hormone, insulin resistance, body mass index (BMI), sugar, creatinine, urea, phosphorus and unsaturated iron binding capacity (UIBC) in blood serum of the group of patients with obesity and comparing with control group, the results showed significant increase in alpine, insulin, insulin resistanse, urea, createnine, glogouse but significant decrease in uibc, bmi. The results also showed a positive correlation between Apelin and insulin, urea, creatinine, phosphorus and a negative correlation between Apelin and insulin resistance, glucose, UIBC, BMI.

***Keywords*---**Obesity, Body mass index, Apelin, Insulin hormone and Insulin resistance.

Introduction

Obesity

The prevalence of overweight and obesity has been increasing significantly in recent decades(F. Ekinci, et al. 2018), have become major global public health

problem (S. Vandevijvere, et al. 2015) and a social problem especially in developed countries, with an increasing incidence in adults and children, and it is associated with low-grade inflammation in white adipose tissue. According to recent data, there are approximately 500 million obese adults worldwide(M. C. Tilinca et al. 2018). Obesity is a multifactorial condition that can be related to nutritional alteration, genetic, psychological and socioeconomic factors, and sedentary lifestyle (Sant'Anna Jr M, et al. 2019). The World Health Organization (WHO) now considers obesity as a global epidemic around the entire world, and it is become one of the most common disorders encountered in medical practices and has major public health implications(M. ALBashtawy, 2017).

Overweight and obesity are defined by WHO as abnormal or excessive fat accumulation that may impair health (WHO,2021). Obesity is a chronic metabolism-related disorder and it is correlated with various pathological conditions that contribute to premature death such as hypertension, atherosclerosis, cardiovascular disease, hyperlipidemia, and diabetes mellitus and certain types of cancers(Javaid F. et. al., 2021),(N. Sattar, et. al.2020),(X Song, et al., 2012),(Yarnell, J. 2009).

BMI

Obese patients are defined as patients with BMI more than 30 (E. Yildiz et al. 2021)., body mass index (BMI) is a widely accepted and arguably the simplest method of measuring overweight and obesity, computed by dividing the weight in kilograms by the square of the height in meters (kg/m2). For an adult, WHO classifies BMI values between 18.5 kg/m² and 24.9 kg/m² as normal or healthy weight, values between 25 kg/m² and 29.9 kg/m² as overweight and values over 30 kg/m² as obese. A BMI of 40 kg/m² or above denotes morbid obesity; under 18.5 kg/m² is considered underweight (Matthias Helble and Azusa Sato,2018),(K. M. Flegal, et. al.,2005).

Apelin

Apelin (APLN) is a recently described adipokine mainly produced by adipose tissue. It is translated as a 77-amino acid prepropeptide precursor and cleaved into shorter peptides (e.g., APLN-13, APLN-17 and -36). However APLN-13 displays much greater biological potency than APLN-36(J. Roche, et al., 2017),(D. Cirakoglu, et al., 2021). More specifically, the apelin-13 isoform demonstrates the greatest capacity to regulate the cardiovascular system (Folino A., et al., 2015). The discovery of apelin as a physiologically active peptide hormone was made after the initial discovery of the apelin receptor (APJ) in 1993 (O'Dowd, B. F.;et al., 1993).

Apelin is considered as one of the novel therapeutic target in cardiovascular research due to its protective actions, has powerful positive inotropic actions(X.H. Yu, et al., 2014), including roles in cardiovascular regulation, body fluid homeostasis(Pitkin, S. L. et al., 2010),(Narayanan, S., et al., 2015). Apelin peptides and the apelin receptor represent a relatively new therapeutic axis for the potential treatment of cardiovascular disease, particularly in view of its beneficial effects on the cardiovascular system(O'Carroll A.M., et al., 2013).

Several reports suggest apelin receptor activation with apelin peptides results in cardioprotection as noted through positive inotropy, angiogenesis, reduction of mean arterial blood pressure, and apoptosis(Narayanan, S., et al., 2015).

Insulin hormone

Insulin is a hormone secreted by β-cells of islets of Langerhans(M.S. Rahman, et al., 2021), controls the metabolism of carbohydrates, proteins, and fats by stimulating the absorption of molecules like glucose from the blood into fat, skeletal muscle cell, and liver (Y. T. Wondmkun,2020). Insulin has polypeptide structure. It can bind to receptors in surface of cells. In brief, insulin is necessary for glucose carrying in tissues (D. Ünal, et al., 2012). Insulin hypersecretion by the pancreas plays a role in the pathogenesis of some forms of obesity (E. Isganaitis, R. H. Lustig, 2005).

Insulin resistance

(IR) is defined as the decreased ability of tissues to respond to insulin action(U. J. Jung and M. S. Choi, 2014) or as inability to control hepatic glucose production and enhance glucose clearance in target tissues(H. Nuru et al.,2017). The prevalence of insulin resistance and type 2 diabetes is rising sharply in nearly all nations globally (F. Imamura, et al.,2016), One of the key health problems associated with obesity is insulin resistance, can lead to a host of serious chronic diseases. The homeostasis model assessment-estimated insulin resistance (HOMA-IR), has been widely used for the estimation of insulin resistance in research(H. Qu, et al., 2011). HOMA-IR calculated by using the following formula: fasting glucose (mg/dL) X fasting insulin (μU/mL)/405 (for SI units: fasting glucose (mmol/L) X fasting insulin (μU/L)/22.5). A value greater than 2 indicates insulin resistance. There is a small difference in cutoff values of HOMA-IR in various studies.(D. Bhosle, et al., 2016).

Aim of the reserch:

Estimate Apelin and Insulin hormone levels in obese patients in comparing with control group and study its relationship with some biochemical parameters.

Materials and Methods

This study was conducted during the period of September 2021 to February 2022, which is the period of case - control study. Clinical and laboratory evaluations were carried out: clinical (recording age, measurement of height, weight, personal and family medical history) and laboratory (various biochemical parameters), blood samples were collected from patients with varying obesity (93 samples) and compared with the control group (24 samples) in the Al-Salam teaching hospital in Mosul City, the study obtained the approval of the ethical research committee in the Nineveh Health Department in Mosul, about 10 ml of venous blood sample was withdrawn from patients and the control group, and the serum was separated by centrifugation at a rate of (3000 rpm) for 15 minutes. A sample of serum was collected of each patient and then stored at -20^{o}C degrees. To perform a homogeneous assessment of parameters for all patients. Serum was separated and used to estimate the following parameters:

1. Apelin hormone was measured by Enzyme-Linked Immunosorbent Assay (ELISA) technique using bioassay technology laboratory (BT Lab), china, with a detection rage between 7-1500 ng/ml, Cat.No E2014Hu.
2. Insulin hormone: insulin levels were measured after an overnight fast of >8 h. using a Electrochemiluminescence immunoassay(ECLIA), (12017547122; Roche Diagnostics)
3. Glucose : was determined by using Abbott ARCHITECT PLUS c4000 device, USA (SN=C460240), (LOT,59255UQ03).
4. Insulin resistance (HOMA-IR): was measured by fasting glucose and fasting insulin using the equation: [fasting glucose(mmol/l) x fasting insulin(μIU/l)/22.5], (H. Nuru et al.,2017).
5. Urea: was determined by using Abbott ARCHITECT PLUS c4000 device, USA (SN=C460240), (LOT,29144UD00).
6. Creatinine: was determined by using Abbott ARCHITECT PLUS c4000 device, USA (SN=C460240), (LOT,33921UD00).
7. Phosphorus: was determined by using Abbott ARCHITECT PLUS c4000 device, USA (SN=C460240), (LOT,04433UN19).
8. Unsaturated Iron Binding Capacity (UIBC): was determined by using Abbott ARCHITECT PLUS c4000 device, USA (SN=C460240), (LOT,90215Y600).
9. Body Mass Index (BMI): was calculated as weight in kilogram divided by square height in meters [A. A. ALhaboo and L. F. Bdaiwi,2021].
   BMI (Kg/m^2) = Wieght (Kg) / Hight(m^2).

Results and discussion

Table (1)
Levels of hormones Apelin, Insulin and some biochemical parameters in serum of patients with obesity for different age groups in compared to the control group.

Hormones and some parameters	Age group (Mean± Standard Deviation)					
	Age group(20-35)year		Age group(36-50)year		Age group(51-65)year	
	Patients group (obese only) (n=24)	Control group (n=10)	Patients group (obese only) (n=38)	Control group (n=7)	Patients group (obese only) (n=2)	Control group (n=7)
Apelin hormone (ng/ml)	179.75±55.903	816.0±55.8	178.815±50.876	1096.1±613.7	204.000±5.656	370.71±308.7
Insulin hormone	5.49 ±1.59	5.24 ±2.308	5.156±1.997	4.82±1.644	6.030±4.299	5.42±1.72
Glucose	96.66±18.069	90.00±9.10	97.578±13.921	88.85±11.15	103.57±6.67	103.50±17.67
Insulin resistance	1.28±0.702	1.17±0.30	1.287±0.487	1.16±0.518	1.630±1.357	1.57±0.49
Urea	22.79±5.356	21.8±6.28	23.394±5.499	32.42±9.94	26.500±3.535	27.42±5.15
Creatinine	0.672±0.105	0.64±0.14	0.697±0.098	1.00±0.56	0.915±0.473	0.73±0.11
Phosphorus	2.983±0.458	3.08±0.345	2.87±0.457	2.907±0.592	2.800±0.565	3.24±0.335
UIBC	217.583±45.477	216.6±49.55	236.44±60.414	220.85±42.67	221.85±74.76	210.00±19.799
BMI (kg/m2)	34.895±3.565	22.73±1.61	37.373±6.116	22.91±1.29	32.30±1.414	23.47±1.59

*APLINE results in table1 show decrease levels of apline in obesity patients in comparism with healthy people in all different age groups.

*INSULIN results in table 1 show decrease in levels of INSULIN in obesity patients in comparism with healthy people in all different age groups.
*gloucose results in table 1 show increase levels of GlOUCOSE in obesity patients in comparism with healthy people in all different age groups.
*Insulin resistance results in table 1 show increase levels of INSULINE resistance in obesty patients in comparism with healthy people in all different age.
*phosphurs results in table 1 show decrease PHOSPHURS levels resistance in obesty patients in comparism with healthy people in all different age.
*uibc results in table 1 show increase levels UIBC in obesty patients in comparism with healthy people in all different age.
*bmi results in table 1 show increase levels of BMI in obesty patients in comparism with healthy people in all different age.

Table (2)
Levels of hormones Apelin, Insulin and some biochemical parameters in serum of patients with obesity with Blood pressure for different age groups and compared to the control group.

Hormones and some parameters	Age group (Mean± Standard Deviation)					
	Age group(20-35)year		Age group(36-50)year		Age group(51-65)year	
	Patients group (obese only) (n=24)	Control group (n=10)	Patients group (obese only) (n=38)	Control group (n=7)	Patients group (obese only) (n=2)	Control group (n=7)
Apelin hormone (ng/ml)	132.00±15.588	816.0±55.8	175.66±59.428	1096.1±613.7	207.000±5.656	370.71±308.7
Insulin hormone	5.49 ±1.59	4.483±1.675	5.40±2.148	4.82±1.644	8.344±5.308	5.42±1.72
Glucose	103.33±21.361	90.00±9.10	95.66±7.68	88.85±11.15	103.57±16.62	103.14 ±6.67
Insulin resistance	1.100±0.293	1.17±0.30	1.194±0.464	1.16±0.518	2.08±1.37	1.57±0.49
Urea	18.66±4.041	21.8±6.28	25.55±8.77	32.42±9.94	35.142±6.59	27.42±5.15
Creatinine	0.600±0.160	0.64±0.14	0.7622±0.067	1.00±0.56	0.891±0.263	0.73±0.11
Phosphorus	2.966 ±0.513	3.08±0.345	3.00±0.661	3.01±0.457	3.24±0.335	3.38±0.267
UIBC	143.12±28.847	89.72±28.33	154.653±34.429	108.12±15.91	147.245±26.828	103.06±30.23
BMI (kg/m2)	35.90±5.534	22.73±1.61	37.477 ±5.855	22.91±1.29	36.94±4.703	23.47±1.59

*Apline results in table2 show decrease levels of Apline in obesity patients with hight blood pressure in comparism with healthy people in all different age groups.

*Insuline results in table 2 show decrease in levels of Insulin in obesity patients with hight blood pressure in comparism with healthy people in all different age groups

*Gloucose results in table 2 show increase levels of Gloucose in obesity patients with hight blood pressure in comparism with healthy people in all different age groups.

*Insulin resistance results in table 2 show increase levels of Insuline resistance in obesty patients with hight blood pressure in comparism with healthy people in all different age.

*Phosphurs results in table 2 show decrease Phosphurs levels resistance in obesty patients with hight blood pressure in comparism with healthy people in all different age.

*UIBC results in table 2 show increase levels UIBC in obesty patients with hight blood pressure in comparism with healthy people in all different age.

*BMI results in table 2 show increase levels of BMI in obesty patients with hight blood pressure in comparism with healthy people in all different age.

Table (3)
Levels of hormones Apelin, Insulin and some biochemical parameters in serum of obese with diabetes mellitus patients for different age groups in compared to the control group.

Hormones and some parameters	Age group (Mean± Standard Deviation)					
	Age group(20-35)year		Age group(36-50)year		Age group(51-65)year	
	Patients group (Obesity with Diabetes mellitus) (n=6)	Control group (n=10)	Patients group (Obesity with Diabetes mellitus) (n=6)	Control group (n=7)	Patients group (Obesity with Diabetes mellitus) (n=3)	Control group (n=7)
Apelin hormone (ng/ml)	175.14±28.3	816.0±55.8	257.33±153.29	1096.1±613.7	370.71±308.7	410.0±259.80
Insulin hormone (ng/ml)	5.49±1.59	9.41±6.30	4.82±1.644	6.705±2.717	5.42±1.72	9.85±4.946
Glucose (mg/dl)	202.0±0	90.00±9.10	225.63±69.94	88.85±11.15	195.0±65.82	103.57±6.67
Insulin resistance	4.87±3.09	1.17±0.30	3.43±0.917	1.16±0.518	3.86±4.353	1.57±0.49
Urea(mg/dl)	25.2±5.02	21.8±6.28	21.66±5.537	32.42±9.94	27.0±2.645	27.42±5.15
Creatinine (mg/dl)	0.64±0.14	0.74±0.05	0.736±0.085	1.00±0.56	0.68±0.13	0.73±0.11
Phosphorus (mg/dl)	3.08±0.345	2.85 ±0.25	2.95±0.361	2.87±0.457	3.30 ±0.60	3.24±0.335
Unsaturated Iron Binding Capacity (UIBC) (ug/dl)	216.6±49.55	216.5 ±45.6	232.83±52.159	220.85±42.67	252.66±88.32	221.85±74.76
BMI (kg/m2)	37.0 ±2.73	22.73±1.61	37.73±3.12	22.91±1.29	32.26±0.550	23.47±1.59

*Apline results in table 3 show decrease levels of APLINE in obesity patients with diabetis meliatus in comparism with healthy people in all different age groups.

*Insulin results in table 3 show decrease in levels of INSULIN in obesity patients with diabeties meliatus in comparism with healthy people in all different age groups.

*Gloucose results in table 3 show increase levels of gloucose in obesity paitient with diabetis meliatus in comparism with healthy people in all different age groups.
*Insulin resistance results in table 3 show increase levels of insuline resistance in obesty patients with diabetis meliatus in comparism with healthy people in all different age.
*Phosphurs results in table 3 show increase phosphurs levels in obesity patients with diabetis meliatus in comparism with healthy people in all different age.

*UIBC results in table 3 show increase levels UIBC in obesity patients with diabetis meliatus in comparism with healthy people in all different age.

*BMI results in table 3 show increase levels of BMI in obesity patients with diabetis meliatus in comparism with healthy people in all different age.

Apelin hormone

The results in tables 1,2,3 showed there was a significant decrease in the levels of apelin in the serum of patients in compared with control group Apelin stimulates glucose uptake in soleus muscle by endothelial nitric oxide synthase-(eNOS), AMP-activated protein kinase-(AMPK), and Akt-dependent pathways. In obese and insulin-resistant mice, apelin also improves glucose uptake in insulin-sensitive tissues underlying a relevant role of apelin in glucose metabolism (Higuchi*, etal* 2007). but low plasma apelin concentrations were reported in patients with newly diagnosed and untreated type 2 diabetes compared with healthy control subjects (4) Recent studies have shown that there is a disorder in the regulation of the expression and secretion of apelin and its receptor (APJ) in the AT of obese and diabetic patients (Alfarano et al., 2015.(

Insulin hormone:

The results in tables 1,2,3 showed there was a significant increase in the levels of insulin in the serum of patients for the different groups in compared with control group Insulin regulates glucose levels in the bloodstream and induces glucose storage in the liver, muscles, and adipose tissue, resulting in overall weight gain. The modulation of a wide range of physiological processes by insulin makes its synthesis and levels critical in the onset and progression of several chronic
diseases. https://www.sciencedaily.com/releases/2009/03/090302115755.htm

Insulin resistance

The results in tables 1,2,3 showed there was a significant increase in the levels of insulin resistance in the serum of patients for the different groups in compared with control group, Because insulin resistance is a precursor of several diseases, it has received considerable attention. Some of the diseases closely connected to insulin resistance are hypertension, type 2 diabetes and CVD (C. B. Breneman and L. Tucker, 2013).

The most important consequence of obesity is the development of insulin resistance. The detection of AT hormones or adipocytokines and changes in the protein levels and gene expressions of these hormones in different tissues, as well as the strong relationship between these alterations and insulin resistance in obese patients, have made some researchers attempt to identify the mechanism of metabolic disorders following obesity and find new treatments. (Kleinz et al., 2005).

Phosphorus

The results in tables 1,2,3 showed there was a significant decrease in the levels of Phosphorus in the serum of patients for the different groups in compared with control group

BMI

On average, women have 6 to 11 percent more body fat than men. Studies show oestrogen reduces a woman's ability to burn energy after eating, resulting in more fat being stored around the body.
oestrogen's effects on postprandial fatty acid oxidation provide a mechanism for fataccumulation(https://www.sciencedaily.com/releases/2009/03/090302115755.htm)

Glougose**:** high apelin levels are associated with decreased risk of development of type diabetes in the general population. The 2possible role of apelin as a biomarker for predicting type 2 diabetes deserve..... studies to assess the usefulness of apelin or apelin analogs as insulin-sensitizing drug.(Diabetes Care 2020;43:e15–e16 | https://doi.org/10.2337/dc19-1865)
Table (4): Effect of sex on patientes with obese only on some biochemical parameters.

Hormones and some parameters	(Mean± Standard Deviation)		sig
	Obese Male	Obese Female	
Apelin hormone (ng/ml)	187.04±53.988	167.304±46.002	0.135
Insulin hormone (ng/ml)	5.4237±2.261	4.8471.914	0.370
Glucose(mg/dl)	99.731±17.392	93.304±10.384	0.066
Insulin resistance	1.394±0.626	1.120±0.496	0.040
Urea(mg/dl)	24.317±5.3737	21.391±4.942	0.034
Creatinine(mg/dl)	0.749±0.106	0.597±0.083	0.000
Phosphorus(mg/dl)	2.961±6.07	2.882±0.393	0.329

Unsaturated Iron Binding Capacity (UIBC) (ug/dl)	218.365±55.894	246.695±48.690	0.038
BMI (kg/m^2)	36.073±5.321	36.665±5.493	0.580

*the parameters results in table 4 show increase in all parameters (Apelin, Insulin hormone , Glucose, Insulin Resistance, Urea , Creatinine , Phosphprus)except of UIBC and BMI women have 6 to 11 percent more body fat than men. Studies show oestrogen reduces a woman's ability to burn energy after eating, resulting in more fat being stored around the body.
oestrogen's effects on postprandial fatty acid oxidation provide a mechanism for fat
accumulation(https://www.sciencedaily.com/releases/2009/03/090302115755.htm)

Table (5)
Effect of sex on obese with Blood pressure patients on some biochemical parameters

Hormones and some parameters	(Mean± Standard Deviation)		sig
	Obese Male with Blood pressure	Obese Female with Blood pressure	
Apelin hormone (ng/ml)	324.444±447.00	167.304±46.002	0.741
Insulin hormone	5.235±1.695	4.847±1.914	0.524
Glucose	93.304±10.385	93.000±6.595	0.141
Insulin resistance	1.186±0.365	1.120±0.496	0.369
Urea	25.555±3.643	21.391±4.942	0.487
Creatinine	0.821±0.121	0.597±0.083	0.130
Phosphorus	3.077±0.491	2.882±0.393	0.065
UIBC	201.222±42.224	246.695±48.690	0.191
BMI (kg/m2)	36.877±3.764	37.13±6.344	0.838

*parameters results in table 5 show increase in all parameters (Apelin , Insulin hormone , Insulin resistance, Urea , Creatinine , Phosphorus , Glucose)except of UIBC and BMI

Table (6)
Effect of sex for obese patients with diabetes mellitus on some biochemical parameters

Hormones and some parameters	(Mean± Standard Deviation)		sig
	Obese Male with Diabetes mellitus	Obese Female with Diabetes mellitus	
Apelin hormone (ng/ml)	306.600±231.941	290.20±191.003	0.851
Insulin hormone	9.287±5.937	7.120±2.756	0.667
Glucose	214.200±62.531	210.00±92.787	0.951
Insulin resistance	4.368±3.319	2.660±1.510	0.353

Urea	23.30±5.012	22.80±6.833	1.000
Creatinine	0.718±0.092	0.656±0.087	0.196
Phosphorus	3.010±0.460	3.300±0.430	0.196
UIBC	237.90±57.933	240.800±79.559	0.854
BMI (kg/m2)	36.410±3.196	36.440±4.473	0.805

*parameters results in table 6 show increase in all parameters(Apelin, Insulin hormone, Insulin resistance, Urea, Creatinine, Glucose) except of UIBC, BMI and Phosphorus

The results in tables 4, 5, 6 showed there was a significant increase in the levels of apelin in male patients with obesity and obesity with blood pressure in compared with female patients while in patients with diabetes mellitus there was a significant decrease in the levels of apelin in male in compared with female. The results in table show 4,5,6 moral increasing in parameters levels[apline ,insulin resistance,urea,creatinine ,phosphorus and gloucose] except[uibc and bmi] in male serm in comparism with female may be as result of testestorone hormone effect which inhibit T-cell.

22 Male androgens play a role in the regulation of adiposity and metabolism. Previous studies have suggested that androgens are inversely associated with fat levels in the visceral and subcutaneous compartments in men.23-25 Although testosterone is positively related to maintenance of healthy body composition and lean muscle mass, it also plays an important role in the deposition of fat to different body regions than seen in women.24,25 These differences in adipose tissue occur in response to determinants of fat uptake and storage. For example, lipoprotein lipase activity plays a role in limiting the accumulation of fat derived from circulating fatty acids and triglycerides. Lipoprotein lipase activity is higher in abdominal/visceral tissues in men because testosterone suppresses enzyme activity in femoral subcutaneous fat.26 On the other hand, enzyme activity is higher in the gluteal/subcutaneous tissues in women.27Therefore, differences in sex hormone levels induce abdominal/visceral obesity in men, while women have more subcutaneous fat but less visceral fat than men.11
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7117999 /

Table (7):
Correlation of Apilen with the other bio chemical parameters

Positive + correlation		Negative - correlation	
Insulin hormone	+	Glucose	-
Urea	+	Insulin resistance	-
Creatinine	+	UIBC	-
Phosphorus	+		
BMI (kg/m2)	+		

*table 7 show Positive + correlation with Apelin with: Insulin, Urea, Creatinine, Phosphorus But inversely proportional of Apelin with: Glucose, Insulin resistance, BMI, UIBC. Apelin increased plasma and adipose tissue apelin expression in obese patients can be reversed by hypocaloric diet associated with weight loss

(Castan-Laurell et al., 2008).

Apelin is increased only obesity associated with hyperinsulinaemia, indicating that obesity or high fat diet feeding may not be the main cause for the rise in the apelin expression thus implies a close relationship between apelin and insulin.[54] (Castan-Laurell I, Vitkova M, Daviaud D, Dray C, Kovacikova M, Kovacova Z, etal)

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