The Lebanese Order of Pharmacists
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معاً للتميّز في رعاية المريض

Case Control Study about the Risk of Pancreatic Cancer with Dipeptidyl Peptidase-4 Inhibitors in Lebanon

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Disclosure

"Jihan H. Safwan" declares to meeting attendees that there are no financial relationships with any for-profit companies that are directly or indirectly related to the subject of this presentation

Learning Objectives

- Review basic concepts related to diabetes mellitus
- Identify novel pharmacotherapeutic drugs for treating diabetes mellitus type 2 (T2DM)
- Apply evidence-based recommendations to pharmacologic treatment interventions of T2DM
- Discuss a case control study about the risk of pancreatic cancer with dipeptidyl peptidase-4 inhibitors in Lebanon

Overview of Diabetes Mellitus

Definition

- Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from:

Defects in Insulin Secretion	Defects in Insulin Action	Or Both

- This may lead to:

- American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2004 Jan;27(suppl 1):s5-s10. Available from: http://dx.doi.org/10.2337/diacare.27.2007.S5
- http://www.cdc.gov/diabetes/pubs/statsreport14/diabetes-infographic.pdf

Classification

- Type 1 Diabetes

- Type 2 Diabetes

- Gestational Diabetes Mellitus (GDM)

Epidemiology

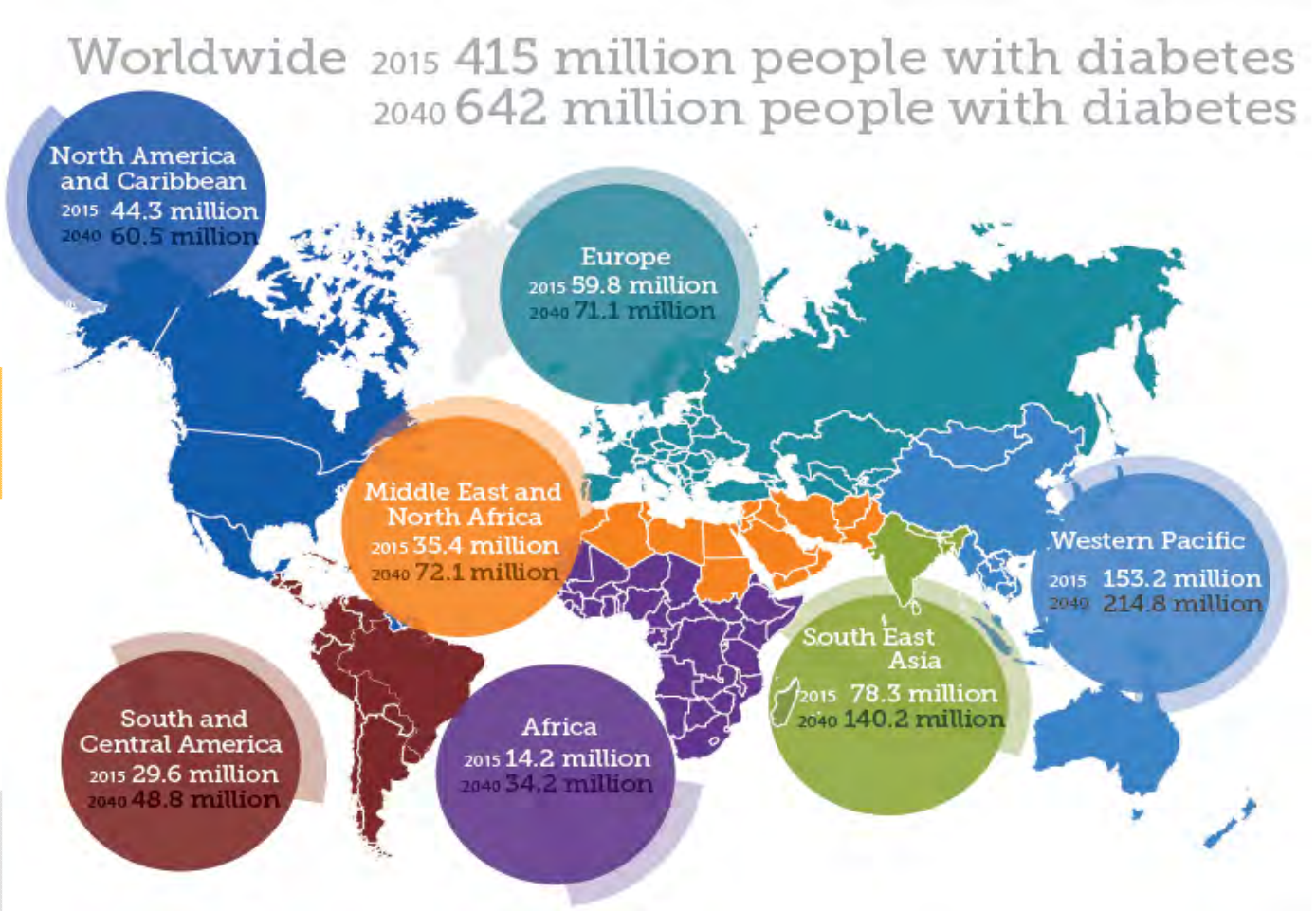
Worldwide public health issue

World Health Organization (WHO)

Prevalence of diabetes in Lebanon could reach 1 in 5 by 2035

International Diabetes Federation (2015)

Lebanon ranks as the 7th country in the MENA area for its high rate of diabetes



Diagnostic Criteria

	Normal	Prediabetes	Diabetes
Fasting Plasma Glucose (FPG)	<100 mg/dL	100 mg/dL to 125 mg/dL	≥126 mg/dL
2-h Plasma Glucose in the 75-g Oral Glucose Tolerance Test (OGTT)	<140 mg/dL	140 mg/dL to 199 mg/dL	≥200 mg/dL
Glycated Hemoglobin (A1C)	<5.7%	5.7–6.4%	≥6.5%
Random Plasma Glucose			≥200 mg/dL plus classic symptoms of hyperglycemia or hyperglycemic crisis

Diabetesed.net. (2018). [online] Available at: https://diabetesed.net/wp-content/uploads/2017/12/2018-ADA-Standards-of-Care.pdf [Accessed 8 Nov. 2018].

Pharmacotherapy for T2DM

Biguanides

- Metformin

Sulfonylureas

2nd Generation

- Glyburide/Glibenclamide
- Glipizide
- Gliclazide
- Glimepiride

Meglitinides

- Repaglinide
- Nateglinide

Thiazolidinediones

- Pioglitazone
- Rosiglitazone

α-Glucosidase Inhibitors

- Acarbose
- Miglitol

Amylin Mimetics

- Pramlintide

Bile Acid Sequestrants

- Colesevelam

Dopamine-2 Agonists

- Bromocriptine (Quick Release)

Diabetesed.net. (2018). [online] Available at: https://diabetesed.net/wp-content/uploads/2017/12/2018-ADA-Standards-of-Care.pdf [Accessed 8 Nov. 2018].

Novel Pharmacotherapy: Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Drugs	Mechanism of Action	Advantages	Disadvantages
Sitagliptin	Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1) concentrations	No hypoglycemia	Heart Failure ➔ Potential risk: saxagliptin & alogliptin
Saxagliptin	↑ Insulin secretion (glucose dependent)	Well tolerated	Acute pancreatitis ➔ Potential risk
Linagliptin	↓ Glucagon secretion (glucose dependent))		High cost
Alogliptin			
Vildagliptin			

5. American Diabetes Association. Standards of Medical Care in Diabetes-2016. Diabetes Care 2016;39(Suppl. 1):S14–S16. Available from: http://care.diabetesjournals.org/content/suppl/2015/12/21/39.Supplement_1.DC2/2016-Standards-of-Care.pdf

Novel Pharmacotherapy: Glucagon-like Peptide 1 (GLP-1) Agonists

Drugs

- Exenatide
- Exenatide ER
- Liraglutide
- Albiglutide
- Dulaglutide
- Lixisenatide

Mechanism of Action

- Activates GLP-1 receptors
- ↑ Insulin secretion (glucose dependent)
- ↓ Glucagon secretion (glucose dependent)
- Slows gastric emptying
- ↑ Satiety

Advantages

- No hypoglycemia
- Weight loss
- ↓ Postprandial glucose excursions
- CVD benefit ➔ FDA approved: Liraglutide

Disadvantages

- Gastrointestinal side effects (nausea/vomiting/diarrhea)
- FDA Black Box: Risk of thyroid C-cell tumors
- Acute pancreatitis risk??
- Injectable
- High cost

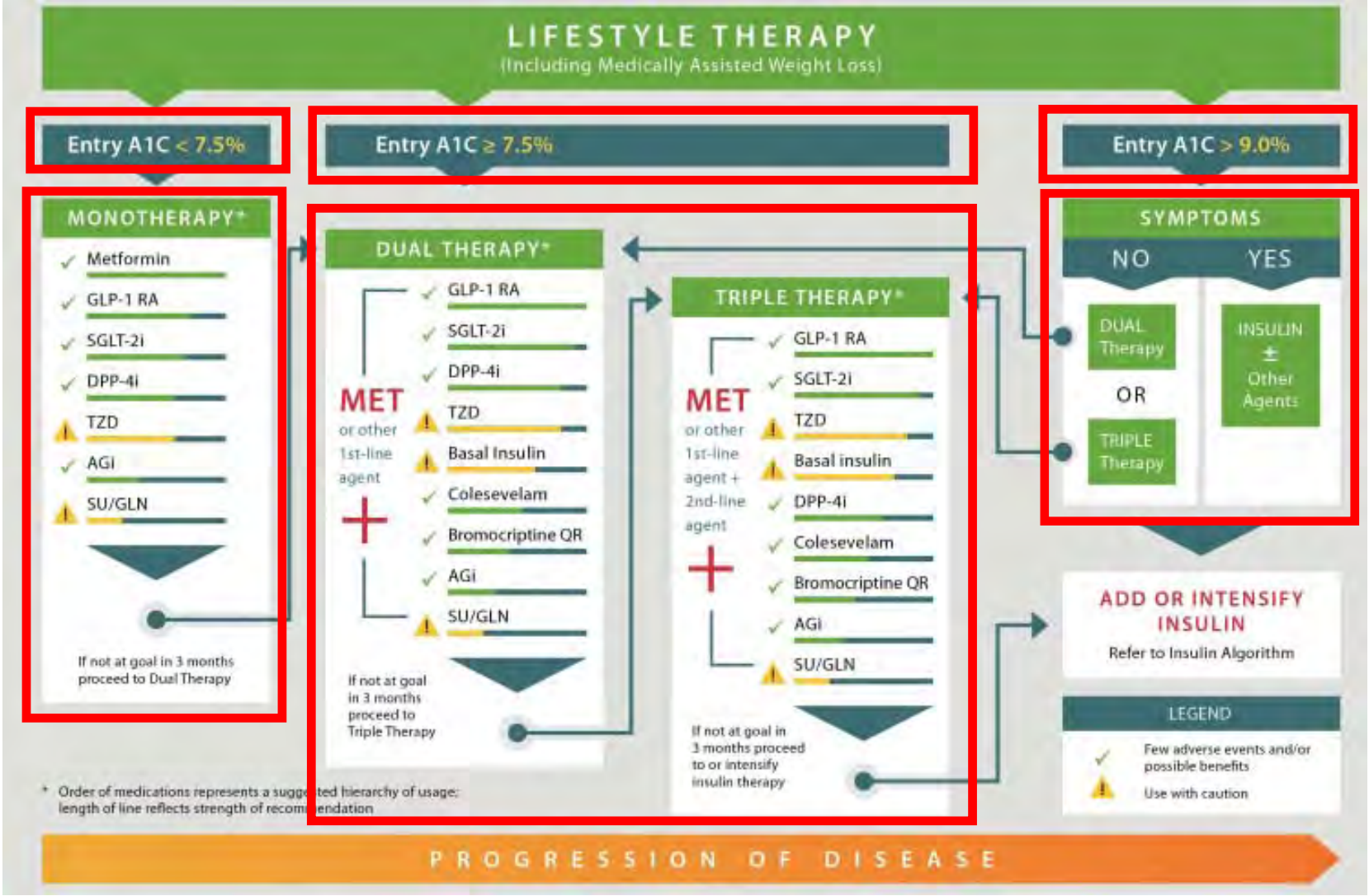
5. American Diabetes Association. Standards of Medical Care in Diabetes-2016. Diabetes Care 2016;39(Suppl. 1):S14–S16. Available from: http://care.diabetesjournals.org/content/suppl/2015/12/21/39.Supplement_1.DC2/2016-Standards-of-Care.pdf

Novel Pharmacotherapy: Sodium–glucose Cotransporter 2 (SGLT2) Inhibitors

Drugs	Mechanism of Action	Advantages	Disadvantages
Canagliflozin	Inhibits SGLT2 in the proximal nephron	No hypoglycemia	Genitourinary infections, polyuria
Dapagliflozin	Blocks glucose reabsorption by the kidney, increasing glucosuria	Weight loss	Volume depletion/ hypotension
Empagliflozin		↓ Blood pressure	↑ LDL-C
		CVD benefit ➔ FDA approved: canagliflozin and empagliflozin	↑ Creatinine (transient)
			UTIs leading to urosepsis, pyelonephritis
			High cost

5. American Diabetes Association. Standards of Medical Care in Diabetes-2016. Diabetes Care 2016;39(Suppl. 1):S14–S16. Available from: http://care.diabetesjournals.org/content/suppl/2015/12/21/39.Supplement_1.DC2/2016-Standards-of-Care.pdf

Type 2 Diabetes Treatment Algorithm



Syllabus.aace.com. (2018). [online] Available at: http://syllabus.aace.com/2017/PNW_Diabetes_Day/Presentations/PDFs/DSouza_Algo_PNW093017PCP.pdf [Accessed 8 Nov. 2018].

Case Control Study about the Risk of Pancreatic Cancer with DPP-4 Inhibitors in Lebanon

Rationale / Outcomes

Rationale

- Risk factors associated with pancreatic cancer are long-term diabetes and smoking
- Risk of pancreatic cancer with DPP-4 inhibitors is controversial
- Such studies are not available in the Middle East or in Lebanon

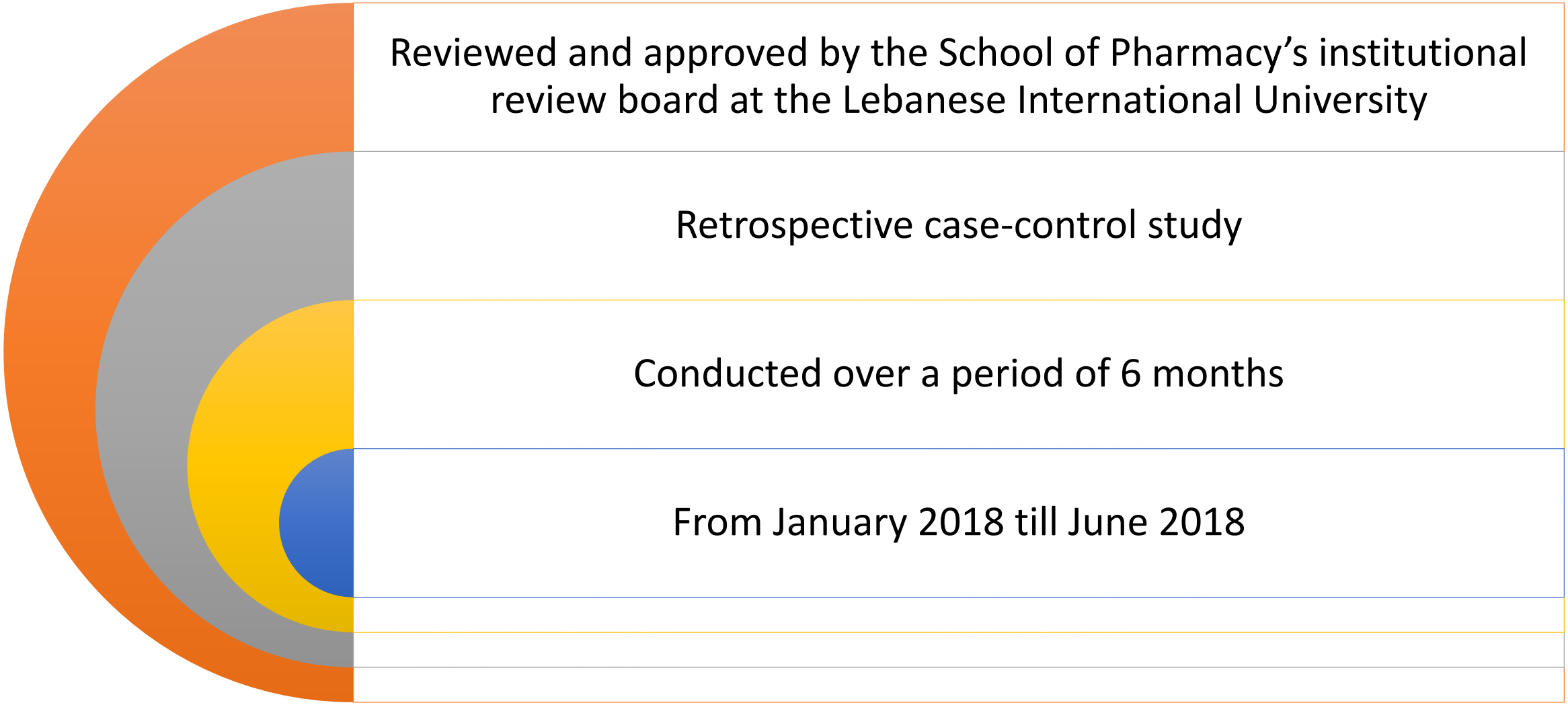
Primary outcome

Evaluate the association between DPP4-Inh and pancreatic cancer risk

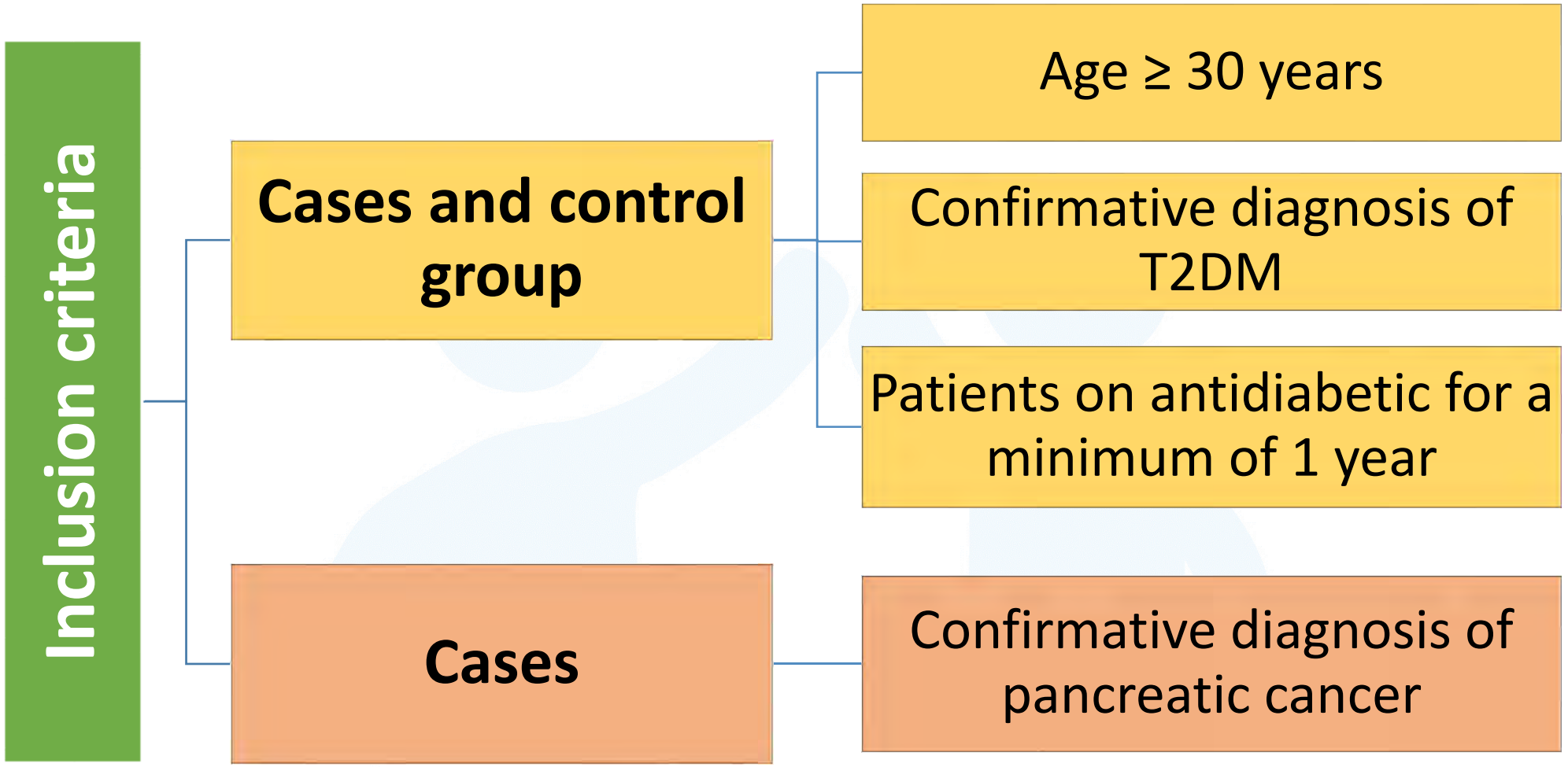
Secondary outcomes

Evaluate the confounding factors affecting our results such as: demographics, social habits, physical activity and co-morbidities

Methodology: Study Design

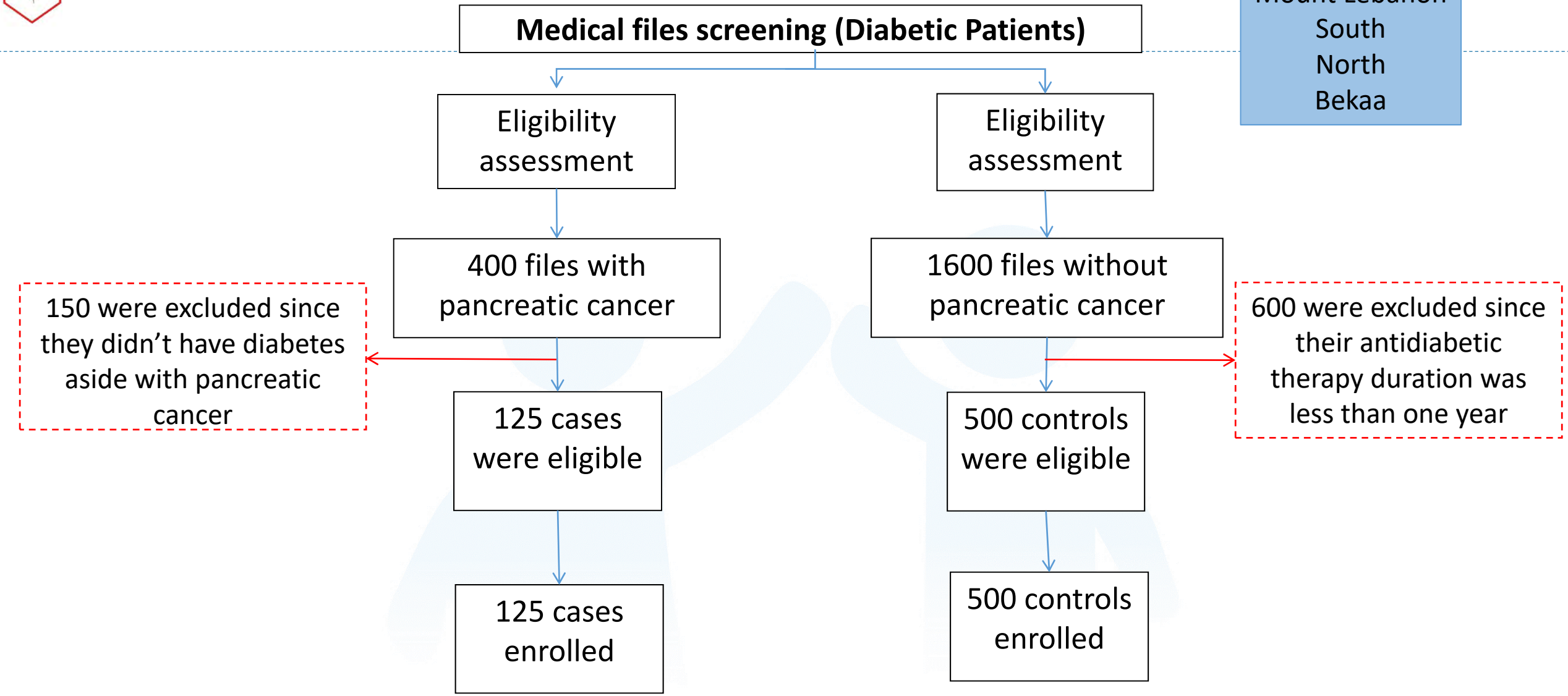


Methodology: Sampling



Methodology : Study Flow Chart

Beirut
Mount Lebanon
South
North
Bekaa



Methodology: Data Analysis

SPSS Software version 21.0

Pearson Chi-square test (or Fisher's exact test)

Student T-test

Unadjusted ORs

Logistic Regression

P-value < 0.05

Results: Demographics

Table 1: Demographics

Characteristic	Controls (n=500)	Cases (n=125)	Unadjusted OR [95% CI]	p-value
Gender (males)	270 (54.0)	68 (54.4)	1.02 [0.69-1.51]	0.936
Age	61.86 ± 30.17	67.93 ± 11.06	1.01 [1.00-1.02]	0.027
BMI	34.38 ± 138.31	29.99 ± 45.64	1.00 [1.00-1.00]	0.756
Marital Status				0.383
Married	434 (86.8)	110 (88.0)	1.44 [0.69-3.01]	0.337
Divorced/Widowed	15 (3.0)	6 (4.8)	2.27 [0.70-7.40]	0.175
Single	51 (10.2)	9 (7.2)	Ref	
Smoking	200 (40.7)	34 (31.5)	0.67 [0.43-1.04]	0.074
Physical activity	249 (50.0)	33 (30.3)	0.43 [0.28-0.68]	<0.001

Results: Co-morbidities

Table 2: Medical history

Characteristic	Controls (n=500)	Cases (n=125)	Unadjusted OR [95% CI]	p-value
History of diabetes (y)	5.03 ± 2.99	6.82 ± 3.35	1.17 [1.10-1.24]	<0.001
Dyslipidemia	239 (47.8)	36 (28.8)	0.44 [0.29-0.68]	<0.001
Hypertension	230 (46.0)	84 (67.2)	2.41 [1.59-3.63]	<0.001
CAD	92 (18.4)	27 (21.6)	1.22 [0.75-1.98]	0.415
COPD	8 (1.6)	5 (4.0)	2.56 [0.82-7.97]	0.150

Results: Medical History

Table 3: Medication history

Characteristic	Controls (n=500)	Cases (n=125)	Unadjusted OR [95% CI]	p-value
Statin	179 (35.8)	30 (24.0)	0.57 [0.36-0.89]	0.012
Other anti-dyslipidemic	80 (16.0)	7 (5.6)	0.31 [0.14-0.69]	0.003
Antiplatelet	130 (26.0)	44 (35.2)	1.55 [1.02-2.35]	0.040
Beta-blocker	116 (23.2)	46 (36.8)	1.93 [1.27-2.93]	0.002
ARB	106 (21.2)	26 (20.8)	0.98 [0.60-1.58]	0.922
ACEI	53 (10.6)	16 (12.8)	1.24 [0.68-2.25]	0.483
CCB	70 (14.0)	13 (10.4)	0.71 [0.38-1.34]	0.289
Diuretic	83 (16.6)	23 (18.4)	1.13 [0.68-1.89]	0.631
Antiseizure	37 (7.4)	17 (13.6)	1.97 [1.07-3.63]	0.027
Stress ulcer prophylaxis	44 (8.8)	45 (36.0)	5.83 [3.61-9.41]	<0.001
Corticosteroid	13 (2.6)	9 (7.2)	2.91 [1.21-6.96]	0.025

Results: Antidiabetic Medications

Table 4: Antidiabetics

Medicine	Controls (n=500)	Cases (n=125)	Unadjusted OR [95% CI]	p-value
Metformin	469 (93.8)	88 (70.4)	0.16 [0.09-0.27]	<0.001
Insulin	51 (10.2)	53 (42.4)	6.48 [4.10-10.25]	<0.001
Rapid acting	7 (1.4)	16 (12.8)	10.34 [4.15-25.74]	<0.001
Short acting	2 (0.4)	9 (7.2)	19.32 [4.12-90.61]	<0.001
Intermediate acting	1 (0.2)	7 (5.6)	29.60 [3.61-242.91]	<0.001
Long acting	33 (6.6)	32 (25.6)	4.87 [2.85-8.31]	<0.001
Premixed	13 (2.6)	5 (4.0)	1.56 [0.55-4.46]	0.378
DPP4-I	286 (57.2)	32 (25.6)	0.26 [0.17-0.40]	<0.001
Vildagliptin	162 (32.4)	12 (9.6)	0.22 [0.12-0.41]	<0.001
Sitagliptin	107 (21.4)	14 (11.2)	0.46 [0.26-0.84]	0.010
Linagliptin	17 (3.4)	2 (1.6)	0.46 [0.11-2.03]	0.392
Saxagliptin	5 (1.0)	4 (3.2)	3.27 [0.87-12.37]	0.084
Teneligliptin	-	-		
Sulfonylurea	207 (41.4)	51 (40.8)	0.98 [0.66-1.45]	0.903
SGLT2-I	41 (8.2)	1 (0.8)	0.09 [0.01-0.66]	0.003
Pioglitazone	31 (6.2)	5 (4.0)	0.63 [0.24-1.66]	0.345
Repaglinide	4 (0.8)	4 (3.2)	4.10 [1.01-16.62]	0.055

Results: Multivariable Analysis

- Performed to identify the factors that were independently associated with pancreatic cancer

- Variables with a p-value < 0.2 in the bivariate analysis were entered hierarchically into the multivariable analysis to build 3 logistic models

Results: Multivariable Analysis

cont'd

Table 5: Multivariable analysis

Variable	Model 1†		Model 2†		Model 3†	
	Adjusted OR [95%CI]	p-value	Adjusted OR [95%CI]	p-value	Adjusted OR [95%CI]	p-value
Physical activity	0.44 [0.27-0.69]	<0.001	0.42 [0.25-0.70]	0.001	0.37 [0.21-0.63]	<0.001
Dyslipidemia	0.34 [0.21-0.55]	<0.001	0.40 [0.24-0.68]	0.001	0.46 [0.27-0.80]	0.005
Hypertension	2.69 [1.69-4.29]	<0.001	2.25 [1.34-3.77]	0.002	2.28 [1.35-3.84]	0.002
COPD	3.44 [0.99-11.87]	0.051	-	-	-	-
History of Diabetes (y)			1.09 [1.01-1.17]	0.021	1.12 [1.04-1.21]	0.003
Insulin			4.38 [2.47-7.75]	<0.001	-	-
DPP4-I			0.33 [0.20-0.55]	<0.001	-	-
SGLT2-I			0.14 [0.02-1.08]	0.059	0.12 [0.02-0.99]	0.050
Long acting insulin					2.95 [1.42-6.12]	0.004
Rapid acting insulin					7.56 [2.48-23.04]	<0.001
Sitagliptin					0.53 [0.27-1.03]	0.061
Vildagliptin					**0.16 [0.08-0.35]**	<0.001

Results: Multivariable Analysis

cont’d

- Results showed a statistically significant association between pancreatic cancer risk and the following factors:

Physical activity

Dyslipidemia

Hypertension

History of Diabetes

Insulin therapy

SGLT2-inhbitors

DPP4-inhibitors

Results: Multivariable Analysis

cont'd

A significantly **increased** risk of pancreatic cancer was shown with **insulin**

- Rapid acting insulin[aOR=7.56, CI (2.48-23.04)] **>** Long acting insulin [aOR=2.95, CI (1.42-6.12)]

DPP-4 inhibitors demonstrated a **lower odds** of pancreatic cancer

- Vildagliptin [(aOR=0.16), CI (0.08-0.35)] **<** Sitagliptin [(aOR=0.53), CI (0.27-1.03)]

Discussion: Risk of Pancreatic Cancer with DPP-4 inhibitors

Assessing Pancreatic Cancer Risk Associated with DPP4-inh

- Elashof analyzed reports from FDA-AERS databases
  - High risk of pancreatic cancer with sitagliptin

Our Study

- No significantly increased risk of pancreatic cancer with DPP4-inhibitors
- Lower odds of pancreatic cancer
  - Vildagliptin < Sitagliptin

FDA-AERS: FDA Adverse Event Reporting System

Feng X, Cai A, Dong K, Chaing W, Feng M, Bhutada NS, et al. Assessing Pancreatic Cancer Risk Associated with Dipeptidyl Peptidase 4 Inhibitors: Data Mining of FDA Adverse Event Reporting System (FAERS). J Pharmacovigil. 2013 Jul 25;1(3):1–7.

Discussion: Risk of Pancreatic Cancer with Other Antidiabetic Medications

University of Texas M.D. Anderson Cancer Center in Houston

- Patients with T2DM who used insulin were 5 times more likely to develop pancreatic cancer

Our Study

- Significantly increased risk with insulin
  - **Rapid acting insulin > long acting insulin**

Insulin may increase risk of Pancreatic Cancer [Internet]. [cited 2018 Jul 20]. Available from: http://www.diabetesspecialist.com/insulin_causes_cancer.html

Discussion: Risk of Pancreatic Cancer with Patients' Co-morbidities

Sitagliptin and pancreatic cancer risk in patients with type 2 diabetes

- Dyslipidemia was significantly associated with an approximately 40% higher risk of pancreatic cancer

Our Study

- Lower odds of pancreatic cancer with dyslipidemia

Sitagliptin and pancreatic cancer risk in patients with type 2 diabetes. - PubMed - NCBI [Internet]. [cited 2018 Jul 20]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26584246

Strengths / Limitations

Strengths

- First case control study in Lebanon
- Use of medical records
- Minimum sample size reached
- Representative data

Limitations

- Missing data in files
- No information related to pancreatic cancer may aggregate in families
- Data collection in Bekaa region concerning alcohol intake ➔ probable inaccuracy due to religious beliefs

Conclusion

This case control study has suggested a protective association between DPP-4 inh and pancreatic cancer, particularly with vildagliptin

It further emphasizes the increased prevalence of pancreatic cancer with insulin therapy

More adequately powered studies are needed to assess the suggested association

THANK YOU