IL PUNTO SUL RISCHIO INFETTIVO NEL DIABETE

Maria Chantal Ponziani

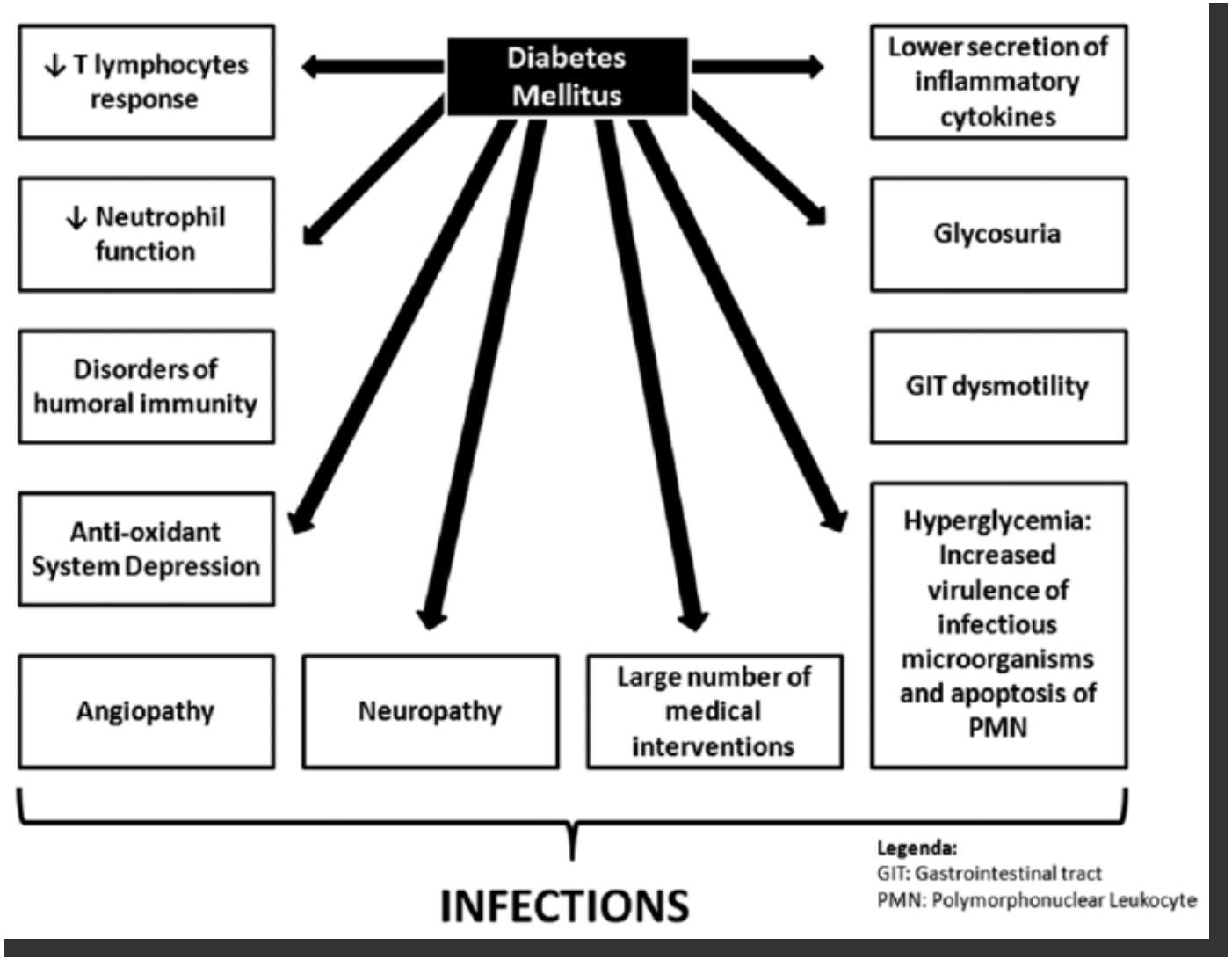
La sottoscritta Maria Chantal Ponziani
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato - Regione del 5 novembre 2009

dichiara

che negli ultimi due anni ha svolto attività di consulenza scientifica per Eli-Lilly,Boehringer Ingelheim

DIABETE E INFEZIONI

- Fattori che predispongono alle infezioni
- Infezioni più frequenti
- Approfondimento su alcune infezioni
- Una rivoluzionaria proposta terapeutica


↓ T lymphocytes response
↓ Neutrophil function
Disorders of humoral immunity
Anti-oxidant System Depression
Angiopathy
Diabetes Mellitus
Neuropathy
Large number of medical interventions
Lower secretion of inflammatory cytokines
Glycosuria
GIT dysmotility
Hyperglycemia: Increased virulence of infectious microorganisms and apoptosis of PMN
INFECTIONS
Legenda:
GIT: Gastrointestinal tract
PMN: Polymorphonuclear Leukocyte

Quantifying the Risk of Infectious Diseases for People With Diabetes

DIABETES CARE, VOLUME 26, NUMBER 2, FEBRUARY 2003

Table 1—*Risk ratios with 99% CIs for the diabetic versus the nondiabetic population for at least one hospitalization or physician claim for an infectious disease*

	1999 Cohort		1996 Cohort	
Diagnosis	Risk ratio (99% CI)	Rate in diabetic population (per 100,000)	Risk ratio (99% CI)	Rate in diabetic population (per 100,000)
All infectious diseases	1.21 (1.20–1.22)*	46,048	1.21 (1.20–1.22)*	47,454
Infectious diseases potentially treatable on an outpatient basis				
Upper respiratory tract infections	1.18 (1.17–1.19)*	28,454	1.18 (1.17–1.19)*	29,558
Cystitis	1.39 (1.36–1.42)*	5,491	1.43 (1.39–1.46)*	5,564
Pneumonia	1.46 (1.42–1.49)*	4,919	1.48 (1.43–1.52)*	4,786
Cellulitis	1.81 (1.76–1.86)*	4,626	1.85 (1.80–1.91)*	4,671
Enteric infections	1.50 (1.46–1.54)*	4,087	1.53 (1.48–1.58)*	4,482
Otitis externa	1.14 (1.09–1.18)*	1,734	1.16 (1.11–1.21)*	1,756
Mycoses	1.38 (1.32–1.44)*	1,396	1.41 (1.34–1.48)*	1,475
Genital infections (male)	0.89 (0.86–0.89)*	1,340	0.94 (0.90–0.98)†	1,583
Otitis media	1.21 (1.15–1.28)*	1,071	1.24 (1.18–1.32)*	1,106
Chicken pox/shingles	1.16 (1.09–1.22)*	816	1.26 (1.17–1.35)*	793
Viral hepatitis	1.49 (1.39–1.60)*	682	1.49 (1.37–1.61)*	661
Pyelonephritis	1.95 (1.78–2.13)*	486	1.86 (1.69–2.05)*	505
Tuberculosis	1.12 (1.03–1.23)†	344	1.21 (1.10–1.35)*	343
Osteomyelitis	4.39 (3.80–5.06)*	340	4.15 (3.54–4.87)*	334
Herpes simplex virus	0.92 (0.84–1.02)	253	0.96 (0.86–1.07)	283
Genital infections (female)	1.16 (1.04–1.30)†	234	1.31 (1.17–1.47)*	287
Mononucleosis	1.60 (1.39–1.85)*	159	1.46 (1.24–1.73)*	148
Rectal abscess	1.97 (1.67–2.32)*	144	2.14 (1.80–2.55)*	170
Mastoiditis	1.06 (0.90–1.24)	99	1.12 (0.96–1.32)	135
Infectious arthritis	1.72 (1.42–2.08)*	98	1.88 (1.52–2.32)*	107
Human immunodeficiency virus	0.96 (0.78–1.18)	57	1.02 (0.80–1.31)	54
Infectious diseases requiring hospitalization				
Sepsis	2.45 (2.23–2.68)*	539	2.54 (2.28–2.82)*	512
Postoperative infections	2.02 (1.80–2.27)*	283	2.31 (2.02–2.64)*	308
Biliary tree infections	1.60 (1.39–1.83)*	173	1.59 (1.36–1.87)*	169
Peritonitis	1.94 (1.58–2.37)*	93	2.40 (1.93–2.99)*	116
Appendicitis	1.19 (0.96–1.47)	62	1.03 (0.80–1.32)	54

*$P < 0.0001$; †$P < 0.001$.

infectious diseases with frequencies >50 1999. Because of failure to match to a such a hospitalization or physician claim.

Table 1: Major infections associated with diabetes mellitus

Respiratory infections
Streptococcus pneumoniae
Influenza
H1N1
Tuberculosis
Urinary tract infections
Asymptomatic bacteriuria
Fungal cystitis
Emphysematous cystitis
Bacterial pyelonephritis
Emphysematous cystitis
Perinephric abscess
Gastrointestinal and liver infections
H. pylori infection
Oral and esophageal candidiasis
Emphysematous cholecystitis
Hepatitis C
Hepatitis B
Enteroviruses
Skin and soft tissue infections
Foot infection
Necrotizing fasciitis
Fournier's gangrene
Head and neck infections
Invasive external otitis
Rhinocerebral mucormycosis
Other infections
Human immunodeficiency virus

Etiology and Outcome of Community-Acquired Pneumonia in Patients With Diabetes Mellitus*

Miquel Falguera, Ricard Pifarre, Antonio Martin, Anas Sheikh and Anna Moreno

Chest 2005;128:3233-3239
DOI 10.1378/chest.128.5.3233

Table 5—*Comparison of Causative Agents in Patients With and Without Diabetes Mellitus

Cause	Diagnosis of Patients With Diabetes (n = 106)			Diagnosis of Patients Without Diabetes (n = 554)		
	Definite	Probable	Total†	Definite	Probable	Total†
Conventional bacteria			44 (42)			246 (44)
S pneumoniae	30	3	33 (31)	180	12	192 (35)
Haemophilus influenzae	2	2	4 (4)	9	2	11 (2)
Staphylococcus aureus	1	2	3 (3)	5	4	9 (2)
Other Gram-negative bacilli	2	0	2 (2)	8	10	18 (3)
Other Gram-positive cocci	2	0	2 (2)	11	3	14 (3)
Anaerobes	0	0	0 (0)	2	0	2 (0.4)
Atypical agents and viruses			32 (30)			196 (35)
C pneumoniae	10	3	13 (12)	42	19	61 (11)
M pneumoniae	3	3	6 (6)	39	13	52 (9)
C burnetii	3	0	3 (3)	7	16	23 (4)
L pneumophila	1	0	1 (1)	26	2	28 (5)
C psittaci	0	0	0 (0)	1	3	4 (1)
Influenza A virus	2	3	5 (5)	11	7	18 (3)
Influenza B virus	2	1	3 (3)	2	2	4 (1)
Adenovirus	1	0	1 (1)	1	1	2 (0.4)
Unknown			41 (39)			161 (29)

*Values are given as No. of patients (%).
†A polymicrobial infection was detected in 10 patients (9%) with diabetes and in 49 patients (9%) without diabetes.

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DOI 10.1378/chest.128.5.3233

Table 1—*Characteristics of Community-Acquired Pneumonia, and Comparison Between Patients With and Without Diabetes Mellitus

Characteristics	Patients With Diabetes (n = 106)	Patients Without Diabetes (n = 554)	p Value
Age, yr	69	54	0.001
Sex			NS
Male	66	359	
Female	40	195	
Pneumonia severity index			
Class I	4 (4)	138 (25)	< 0.001
Class II	14 (13)	154 (28)	
Class III	41 (39)	143 (26)	
Class IV	35 (33)	95 (17)	
Class V	12 (11)	24 (4)	
Concomitant underlying diseases	56 (53)	219 (40)	0.018
Typical clinical picture	42 (40)	262 (47)	NS
WBC count, cells/μL	15100	13430	NS
Bacteremial	10/84 (11)	52/464 (10)	NS
Multilobar infiltrate	15 (14)	106 (19)	NS
Pleural effusion	33 (31)	111 (20)	0.015
Empyema or complicated effusion	9 (8)	42 (8)	NS
Hospitalization	99 (93)	431 (78)	< 0.001
ICU admission	15 (14)	48 (9)	NS
Mortality	18 (17)	40 (7)	0.002
Length of hospital stay,‡ d	10.2	9.1	NS

*Values are given as the mean for continuous variables and as No. (%) for categoric variables, unless otherwise indicated. NS = not significant.
†Blood cultures were not obtained in 50 patients (8%).
‡Outpatients were excluded.

Table 3—*Diabetes-Related Findings and Other Characteristics of Patients With Diabetes Mellitus: Univariate Analysis of Factors Associated With Mortality

Variables	Patients Dead (n = 18)	Patients Alive (n = 88)	p Value
Age, yr	71	68	NS
Sex			NS
Male	10	56	
Female	8	32	
Concomitant underlying diseases	15 (83)	40 (45)	0.004
Period from diagnosis of diabetes			
≤ 4 yr	10 (44)	52 (59)	NS
> 4 yr	8 (56)	36 (41)	
Glucose level at entry (mg/dl)	267	239	NS
Hemoglobin A1c level (%)	8.3	8.1	NS
Major diabetes-related complications			
Retinopathy	4 (22)	16 (18)	NS
Nephropathy	6 (33)	11 (13)	0.040
Vasculopathy	8 (44)	10 (11)	0.002
Peripheral polyneuropathy	1 (6)	4 (5)	NS
Insulin therapy during pneumonia	17 (94)	78 (89)	NS
Bacteremia†	3 (19)	7 (9)	NS
Multilobar infiltrate	7 (39)	8 (9)	0.004
Pleural effusion	7 (39)	26 (30)	NS
Empyema or complicated effusion	3 (17)	6 (7)	NS

*Values are given as the mean for continuous variables and as No. (%) for categoric variables. See Table 1 for abbreviation not used in the text.
†Blood cultures were not obtained in 12 patients (11%).

Etiology and Outcome of Community-Acquired Pneumonia in Patients With Diabetes Mellitus

Miquel Falguera, Ricard Pifarre, Antonio Martin, Anas Sheikh and Anna Moreno

Chest 2005;128:3233-3239
DOI 10.1378/chest.128.5.3233

Table 4—*Multivariate Analyses of Factors Associated With Mortality and Pleural Effusion in Patients With Diabetes Mellitus and Community-Acquired Pneumonia

Variables	Odds Ratio	95% Confidence Interval	p Value
Dependent variable-mortality			
Multilobar infiltrate	8.847	2.147–36.451	0.003
Concomitant underlying diseases†	5.190	1.187–22.690	0.029
Dependent variable-pleural effusion			
Diabetes-related complications			
Nephropathy	25.746	2.202–30.1.015	0.010
Vasculopathy	6.626	1.109–39.582	0.038
Concomitant underlying diseases†	3.247	1.103–9.562	0.033

*Based on 104 (98%) patients for whom complete data were available.

†Includes neoplastic disease, congestive heart failure, cerebrovascular disease, chronic renal disease, chronic pulmonary obstructive disease, chronic liver disease, and HIV infection

Type 2 Diabetes and Pneumonia Outcomes

A population-based cohort study

DIABETES CARE, VOLUME 30, NUMBER 9, SEPTEMBER 2007

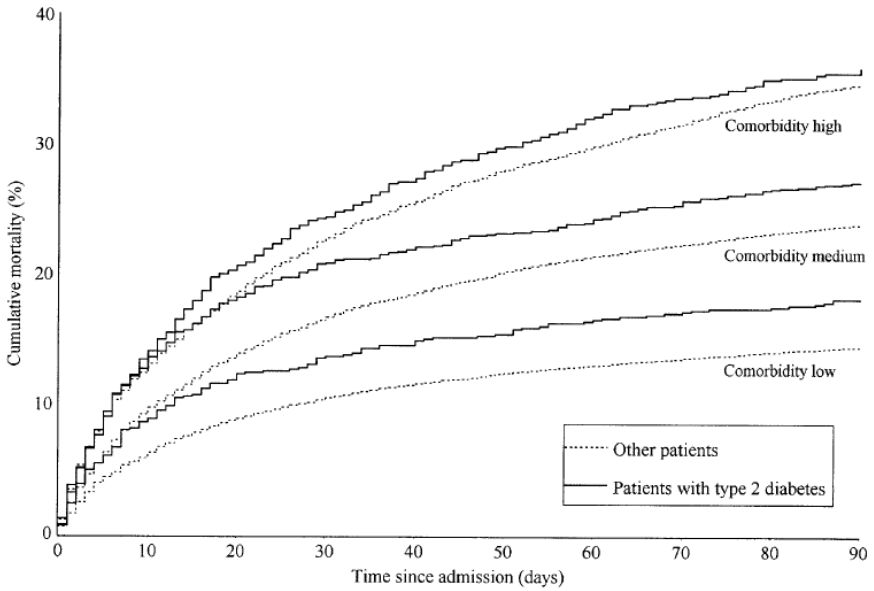


Figure 1—*Mortality curves for patients with type 2 diabetes compared with other patients hospitalized with pneumonia, according to level of Charlson index score.*

Table 2—*Crude and adjusted mortality within 30 and 90 days among patients hospitalized for pneumonia*

Prognostic factor	*n*	Deaths	Mortality (%)	Crude MRR (95% CI)	Adjusted MRR (95% CI)*	*P*
30 day						
No diabetes	26,877	4,048	15.1	1.0 (ref.)	1.0 (ref.)	
Type 2 diabetes	2,931	582	19.9	1.36 (1.25–1.48)	1.16 (1.07–1.27)	<0.01
90 day						
No diabetes	26,877	5,818	21.6	1.0 (ref.)	1.0 (ref.)	
Type 2 diabetes	2,931	791	27.0	1.30 (1.21–1.40)	1.10 (1.02–1.18)	0.02

Data are *n* unless otherwise indicated. *Adjusted for sex, age group, level of comorbidity, alcoholism-related conditions, and use of antibiotics and immunosuppressive drugs before admission.

Table 3—*Crude and adjusted mortality within 30 days among pneumonia patients with available glucose values on admission*

30-day glucose level (mmol/l)	*n*	Deaths	Mortality (%)	Crude MRR (95% CI)	Adjusted MRR (95% CI)*	*P*
All patients	10,414					
≤6.1	5,129	727	14.2	1.0 (ref.)	1.0 (ref.)	
6.11–11.0	4,446	903	20.3	1.49 (1.36–1.65)	1.37 (1.25–1.51)	<0.01
11.01–13.99	383	86	22.5	1.68 (1.35–2.10)	1.49 (1.19–1.86)	<0.01
≥14	456	107	23.5	1.79 (1.46–2.20)	1.71 (1.40–2.10)	<0.01
Patients with type 2 diabetes	1,307					
≤6.1	279	52	18.6	1.0 (ref.)	1.0 (ref.)	
6.11–11.0	545	95	17.4	0.93 (0.66–1.30)	0.96 (0.69–1.35)	0.82
11.01–13.99	188	40	21.3	1.18 (0.78–1.78)	1.24 (0.82–1.88)	0.31
≥14	295	65	22.0	1.24 (0.86–1.78)	1.46 (1.01–2.12)	0.04
Other patients	9,107					
≤6.1	4,850	675	13.9	1.0 (ref.)	1.0 (ref.)	
6.11–11.0	3,901	808	20.7	1.56 (1.41–1.73)	1.43 (1.29–1.59)	<0.01
11.01–13.99	195	46	23.6	1.81 (1.34–2.44)	1.65 (1.23–2.23)	<0.01
≥14	161	42	26.1	2.07 (1.51–2.82)	1.91 (1.40–2.61)	<0.01

Data are *n* unless otherwise indicated. *Adjusted for sex, age group, level of comorbidity, alcoholism-related conditions, and use of antibiotics and immunosuppressive drugs before admission.

Risk of Community-Acquired Pneumococcal Bacteremia in Patients With Diabetes

A population-based case-control study

DIABETES CARE, VOLUME 27, NUMBER 5, MAY 2004

Table 2—*Crude and adjusted OR for community-acquired pneumococcal bacteremia according to presence of diabetes*

Diabetes	Crude OR* (95% CI)	Adjusted OR† (95% CI)
Not present	1.0 (ref.)	1.0 (ref.)
Present	1.9 (1.4–2.6)	1.5 (1.1–2.0)

*Crude OR for presence of diabetes in cases with pneumococcal bacteremia compared with sex- and age-matched control subjects; †OR adjusted for level of comorbidity and alcohol-related disorders (see text).

Table 3—*OR for community-acquired pneumococcal bacteremia according to presence of diabetes, stratified by age, sex, and level of comorbidity*

	Crude OR* (95% CI)	Adjusted OR† (95% CI)
Age (years)		
>15–40	4.3 (1.1–16.6)	4.2 (1.1–16.7)
>40–65	3.2 (1.8–5.7)	2.1 (1.1–3.9)
>65–80	1.5 (0.9–2.5)	1.3 (0.8–2.1)
>80	1.4 (0.8–2.6)	1.2 (0.6–2.2)
Sex		
Male	2.2 (1.4–3.4)	1.8 (1.2–2.8)
Female	1.6 (1.0–2.5)	1.2 (0.8–2.0)
Comorbidity‡		
Comorbidity index low (0)	2.3 (1.3–3.9)	2.3 (1.3–3.9)
Comorbidity index medium (1–2)	0.8 (0.4–1.6)	0.8 (0.4–1.6)
Comorbidity index high (>2)	1.1 (0.3–3.3)	1.1 (0.3–3.3)

*Crude OR for presence of diabetes in cases with pneumococcal bacteremia compared with sex- and age-matched control subjects; †OR adjusted for level of comorbidity (except when stratified by this variable) and alcohol-related disorders (see text); ‡using the Charlson index (see text).

Tuberculosis and diabetes mellitus: convergence of two epidemics

Kelly E Dooley and **Richard E Chaisson**
Division of Infectious Diseases and Center for Tuberculosis Research (K E Dooley MD, R E Chaisson MD), **and Division of Clinical Pharmacology** (K E Dooley), Johns Hopkins University School of Medicine, Baltimore, MD, USA

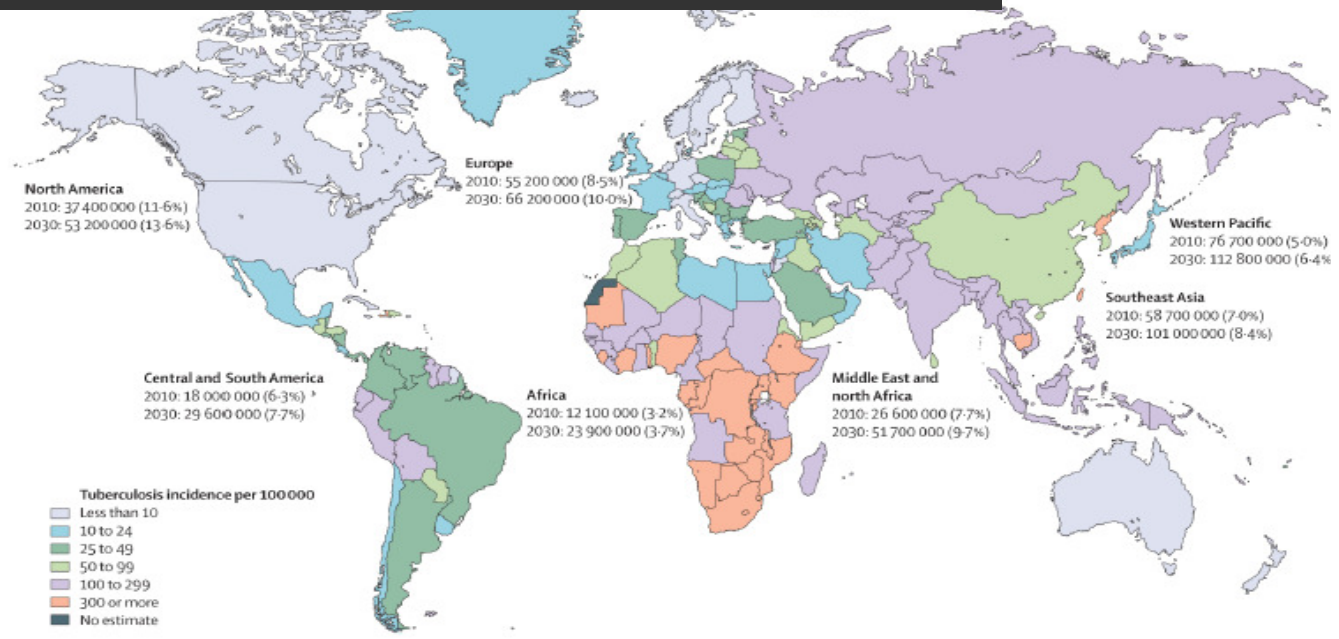
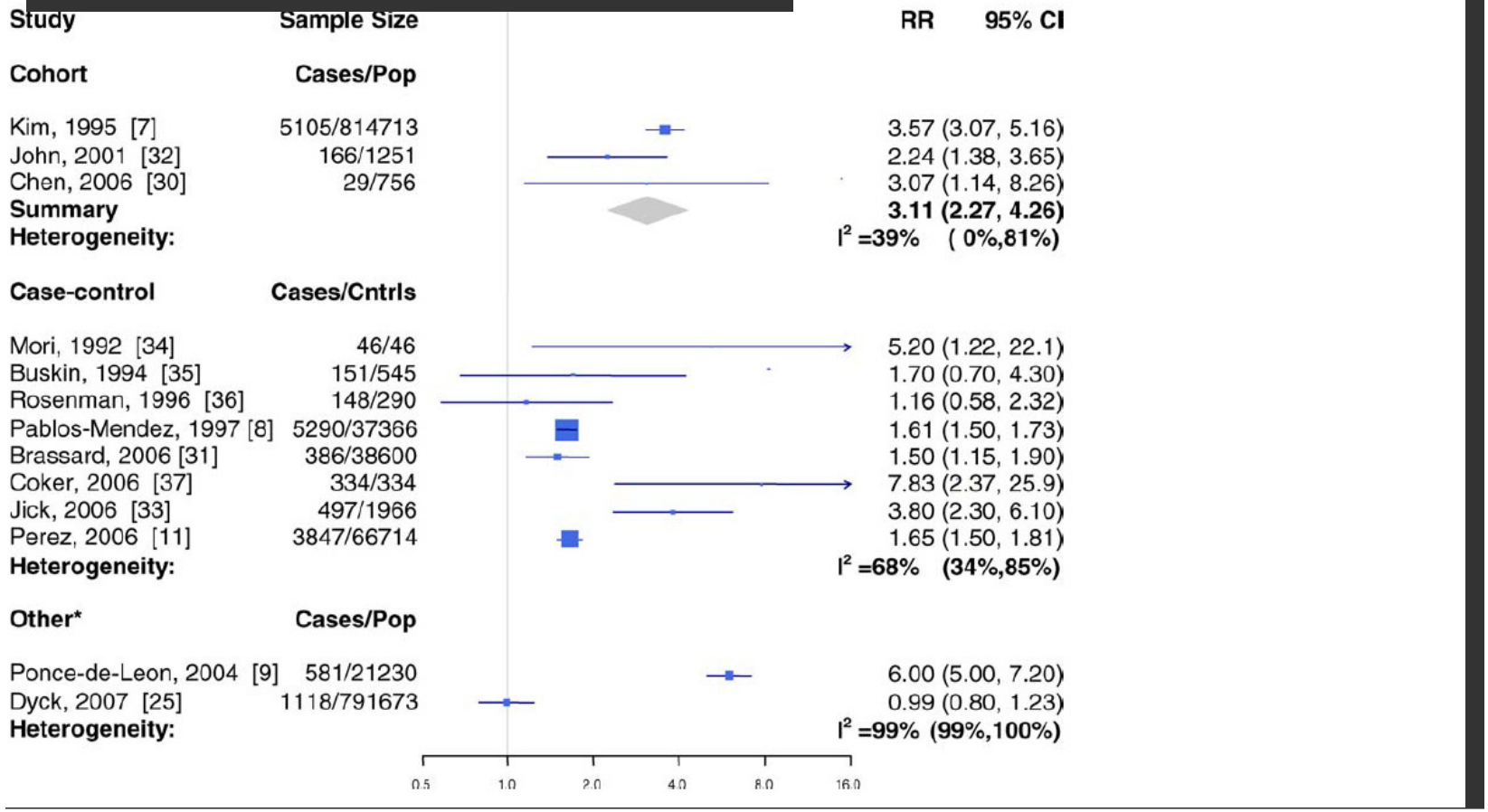


Figure. Projected prevalent diabetes cases and current worldwide tuberculosis incidence
Estimated number and percent of individuals with diabetes mellitus in 2010 compared with 2030 projections are shown. Tuberculosis incidence per 100 000 population data for 2007 are shown. Data from International Diabetes Foundation and WHO.[10,11]

Diabetes Mellitus Increases the Risk of Active Tuberculosis: A Systematic Review of 13 Observational Studies

Christie Y. Jeon*, Megan B. Murray
Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, United States of America



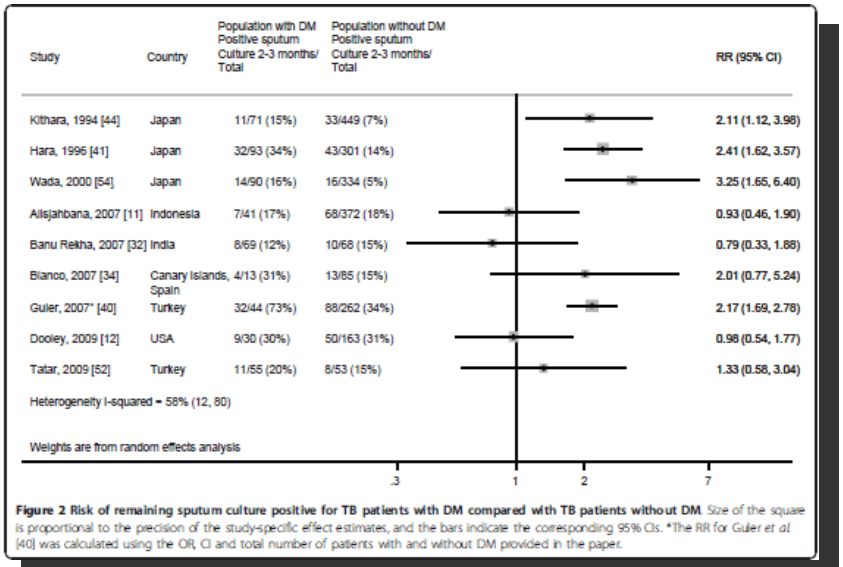


Figure 2 Risk of remaining sputum culture positive for TB patients with DM compared with TB patients without DM. Size of the square is proportional to the precision of the study-specific effect estimates, and the bars indicate the corresponding 95% CIs. *The RR for Guler *et al* [40] was calculated using the OR, CI and total number of patients with and without DM provided in the paper.

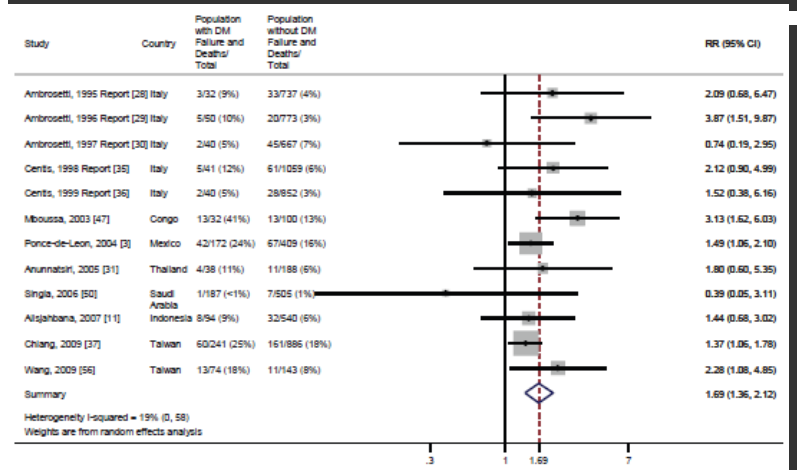


Figure 3 Risk of failure/death for TB patients with DM compared with TB patients without DM. Size of the square is proportional to the precision of the study-specific effect estimates, and the bars indicate the corresponding 95% CIs. The diamond is centered on the summary RR of the observational studies, and the width indicates the corresponding 95% CI.

The impact of diabetes on tuberculosis treatment outcomes: A systematic review

Meghan A Baker[1,2], Anthony D Harries[3,4], Christie Y Jeon[5,10], Jessica E Hart[6], Anil Kapur[7], Knut Lönnroth[8], Salah-Eddine Ottmani[8], Sunali D Goonesekera[2] and Megan B Murray[2,9*]

Baker et al. BMC Medicine 2011, 9:81
http://www.biomedcentral.com/1741-7015/9/81

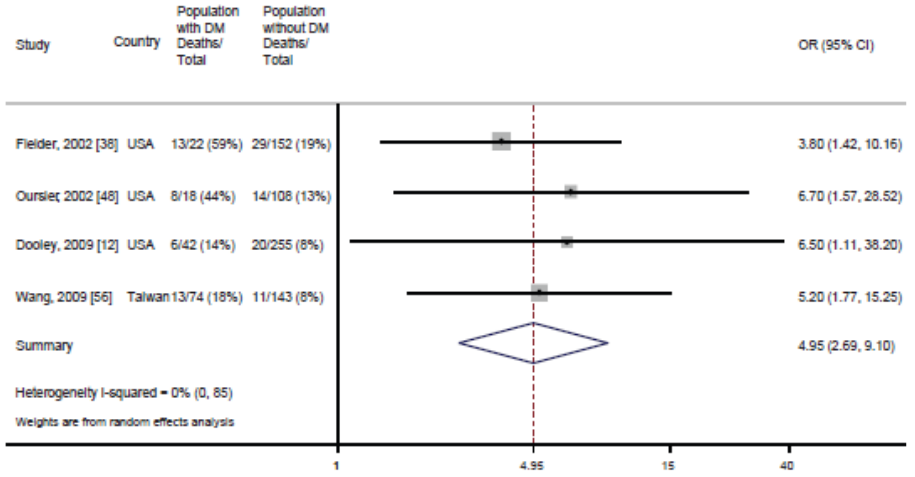


Figure 5 Adjusted odds of death for TB patients with DM compared with TB patients without DM. Size of the square is proportional to the precision of the study-specific effect estimates, and the bars indicate the corresponding 95% CIs. The diamond is centered on the summary OR of the observational studies, and the width indicates the corresponding 95% CI.

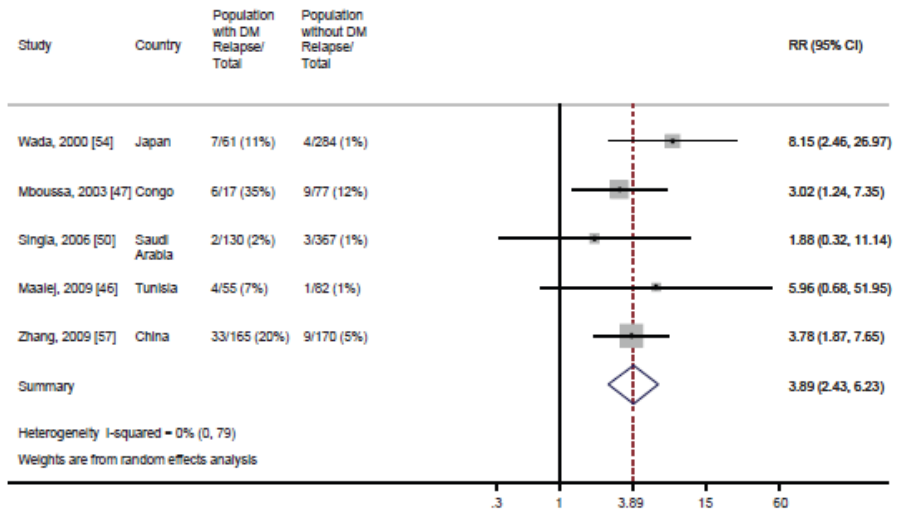


Figure 6 Risk of TB relapse for TB patients with DM compared with TB patients without DM. Size of the square is proportional to the precision of the study-specific effect estimates, and the bars indicate the corresponding 95% CIs. The diamond is centered on the summary RR of the observational studies, and the width indicates the corresponding 95% CI.

The impact of diabetes on tuberculosis treatment outcomes: A systematic review

Meghan A Baker[1,2], Anthony D Harries[3,4], Christie Y Jeon[5,10], Jessica E Hart[6], Anil Kapur[7], Knut Lönnroth[8], Salah-Eddine Ottmani[8], Sunali D Goonesekera[2] and Megan B Murray[2,9*]

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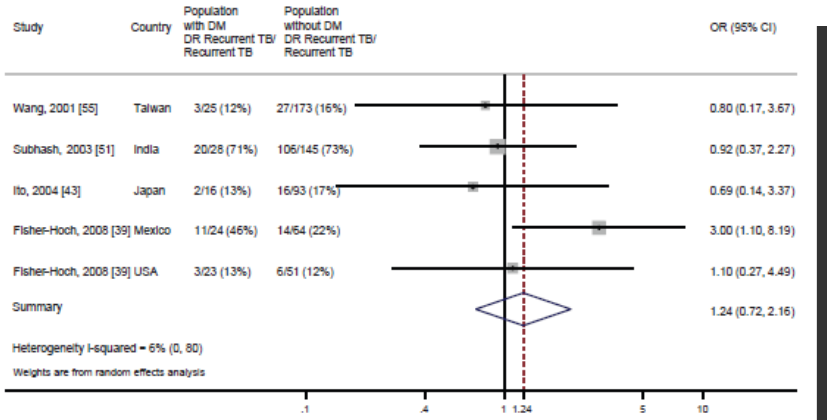

Figure 7 Odds of recurrent TB that is DR, comparing patients with DM to patients without DM. Size of the square is proportional to the precision of the study-specific effect estimates, and the bars indicate the corresponding 95% CIs. The diamond is centered on the summary OR of the observational studies, and the width indicates the corresponding 95% CI.

Urinary tract infections in patients with diabetes mellitus: epidemiology, pathogenesis and treatment

Suzanne E. Geerlings*

Academic Medical Center, F4-217, Center for Infection and Immunity Amsterdam (CINIMA), Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

- Alta prevalenza di batteriuria asintomatica (ASB) in particolare nel sesso femminile (26% vs 6%)
- I soggetti diabetici con microalbuminuria presentano un'aumentata prevalenza di ASB (21% vs 8%)

- Aumentata incidenza di infezioni delle vie urinarie (UTIs) :
  - Diabete mellito tipo 1 OR 1.56
  - Diabete mellito tipo 2 OR 1.21
  - Donne diabetiche postmenopausa OR 2.2

Diabetes Care 2000;26:510
Clin Infect 2005;41:281
Diabetes Care 2002;25:1778
BMC Research Note 2010;3:169

Urinary tract infections in patients with diabetes mellitus: epidemiology, pathogenesis and treatment

Suzanne E. Geerlings*

Academic Medical Center, F4-217, Center for Infection and Immunity Amsterdam (CINIMA), Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

- Nessuna differenza negli agenti eziologici
- Stessa virulenza e resistenza agli agenti antimicrobici in E. Coli isolate da urine di donne diabetiche
- In vitro l'aggiunta di glucosio aumenta la crescita batterica, mentre in vivo la glicosuria non rappresenta un fattore di rischio per ABS o per lo sviluppo di UTIs
- Nessuna differenza nelle funzioni granulocitarie tra donne diabetiche con ASB, donne diabetiche non batteriuriche e controlli sani
- Minori concentrazioni di citochine urinarie in donne diabetiche con ASB rispetto alle donne non diabetiche con ASB

Diabet Med 2004;21:1032
J Med Microbiol 1999;48:535
Diabetes Care 2000;23:1737
Diabetes Care 1997;20:392
Eur J Clin Invest 2000;30:995

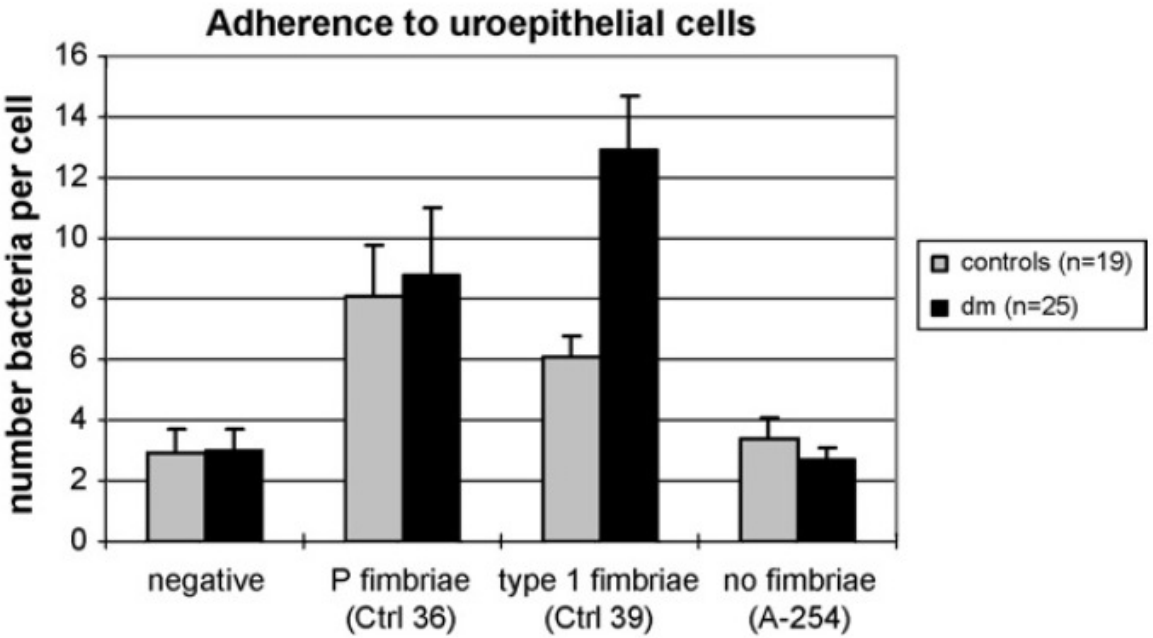

Fig. 1. Mean + standard error of the mean number of adherent bacteria/cell of three *Escherichia coli* strains or negative control on uroepithelial cells isolated from women with and without diabetes mellitus (DM) [16].

Diabetes Care 2002;25:1405

***Helicobacter pylori* infection and endocrine disorders: Is there a link?**

Konstantinos X Papamichael, Garyphallia Papaioannou, Helen Karga, Anastasios Roussos, Gerassimos J Mantzaris

World J Gastroenterol 2009 June 14; 15(22): 2701-2707
World Journal of Gastroenterology ISSN 1007-9327

- La relazione tra DM e infezione da H Pylori è controversa
- Molti studi hanno documentato una elevata prevalenza dell'infezione sia nel DM1 sia nel DM2, correlata con durata di malattia , neuropatia autonomica, BMI, pressione arteriosa e livelli di HBAIc
- Altri studi non hanno documentato differenze di prevalenza tra diabetici e non diabetici e nessuna correlazione con le complicanze della malattia

Dig Dis Sci 1996;41:458
New Microbiol 1996;19:149
Eur J Gastroenterol Hepatol 1998;10:469
J Endocrinol Invest 2005;28: 214
Nutr Metab Cardiovasc Dis 2000;10:263
Eur J Intern Med 2002;13:376
Rev Med Chir Scoc Med Iasi 2003;107:59

Helicobacter pylori infection and endocrine disorders: Is there a link?

Konstantinos X Papamichael, Garyphallia Papaioannou, Helen Karga, Anastasios Roussos, Gerassimos J Mantzaris

World J Gastroenterol 2009 June 14; 15(22): 2701-2707
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- Tutti gli studi concordano nel sottolineare una minore efficacia della terapia eradicante e un tasso particolarmente elevato di re-infezioni soprattutto nel DM2 rispetto alla popolazione generale
- I soggetti con diabete di tipo 1 raggiungono un minore tasso di eradicazione in corso di triplice terapia standard rispetto ai soggetti di tipo 2
- Viene riportato un aumento del fabbisogno insulinico in bambini affetti da DM1 e H pylori

Min Med 2001;92:137
Eur J Gastroenterol Hepatol 1999;11:713
Scand J Gastroenterol 2000;35:260
World J Gastroenterol 2003;9:1126
Pediatrics 1999;103:e83

Seroprevalence of hepatitis C in type 2 diabetes: evidence for a positive association

Nauman A Jadoon*, Mohammad A Shahzad, Rehan Yaqoob, Mansoor Hussain, Naseema Ali

Jadoon *et al. Virology Journal* 2010, **7**:304
http://www.virologyj.com/content/7/1/304

- Molti studi hanno evidenziato una elevata prevalenza di HCV sieropositività nei soggetti con DM2 con riscontro di un rischio da 2 a 7 volte superiore
- Dopo correzione per fattori confondenti uno studio condotto in USA ha documentato come i soggetti HCV + presentassero un rischio 3.77 volte maggiore di essere diabetici
- In uno studio condotto in Pakistan la HCV sieropositività è risultata 13.7% nel DM2 vs 4,9% in assenza di diabete

Hepatology 1999;29:328
J Clin Med Assoc 2006;69:146
Hepatology 2001;33:1554
Virology Journal 2010;7:304

Impaired IRS-1/PI3-Kinase Signaling in Patients With HCV: A Mechanism for Increased Prevalence of Type 2 Diabetes

Serhat Aytug,[1] David Reich,[2] Lawrence E. Sapiro,[1,3] David Bernstein,[4] and Najma Begum[1,3]

HEPATOLOGY, Vol. 38, No. 6, 2003

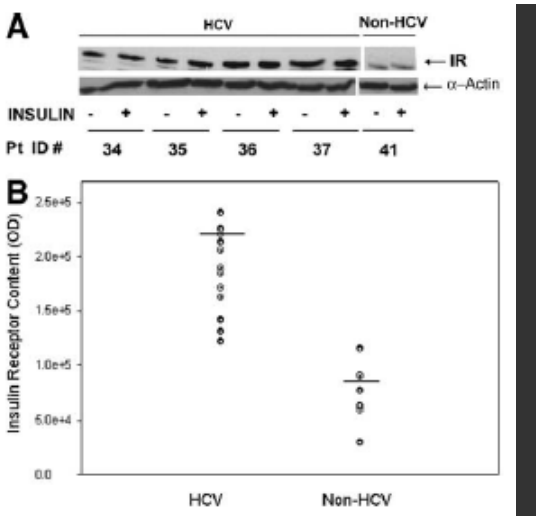


Fig. 1. Comparison of hepatic IR content in HCV-infected subjects and non-HCV-infected controls. Human liver biopsy specimens were treated with and without insulin (100 nmol/L for 10 minutes). Equal amounts of homogenate proteins (100 μg) were subjected to 7.5% SDS-PAGE, and proteins were transferred to polyvinylidene difluoride membranes and probed with anti-IR β subunit antibodies. (A) A Western blot from a representative experiment is shown. The bottom portion of the blot was probed for α-actin, which served as a loading control. (B) ECL signals from HCV and non-HCV samples were quantitated by densitometric scanning, and the intensity of signal that represents IR content was plotted. Results are the mean ± SEM of 42 non-HCV-infected and 10 HCV-infected subjects.

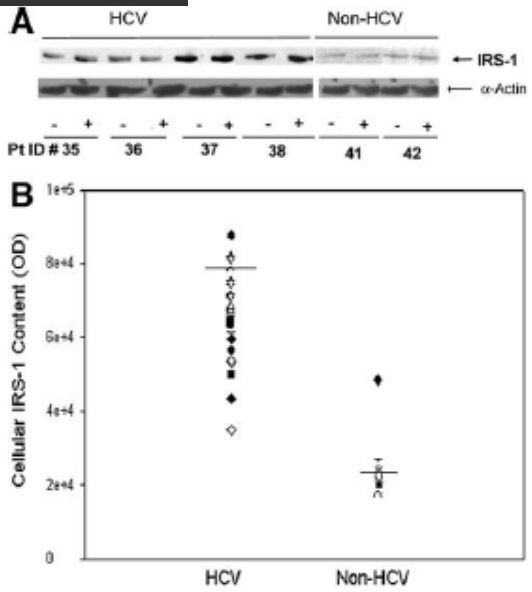


Fig. 2. HCV infection is accompanied by increased hepatic IRS-1 protein levels. Equal amounts of liver homogenates were subjected to SDS-PAGE followed by Western blot analysis. The top portion of the membranes was probed with anti-IRS-1 antibody and the bottom portion with anti-α-actin antibody. (A) A representative Western blot is shown. (B) Quantitation of IRS-1 protein from multiple samples by densitometric analysis of linear ECL signals. Results are the mean ± SEM of non-HCV and HCV liver samples.

Aumento di 3 volte nel contenuto di recettori insulinici (IR) e di 2-6 volte nel contenuto di IRS 1

Impaired IRS-1/PI3-Kinase Signaling in Patients With HCV: A Mechanism for Increased Prevalence of Type 2 Diabetes

Serhat Aytug,[1] David Reich,[2] Lawrence E. Sapiro,[1,3] David Bernstein,[4] and Najma Begum[1,3]

HEPATOLOGY, Vol. 38, No. 6, 2003

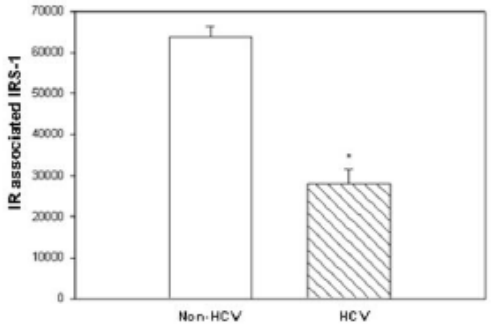


Fig. 4. HCV infection is accompanied by impaired IRS-1 association with the IR. Liver specimens were treated with and without insulin as detailed in the legend to Fig. 1. Equal amounts of homogenate proteins (4 mg) pooled from 4 HCV-infected patients each and 3 non-HCV-infected subjects each were immunoprecipitated at 4°C overnight with anti-IRβ antibody (10 μg) followed by addition of 100 μL protein A Sepharose beads (vol/vol). Tubes were incubated for an additional hour with constant mixing on a rotator. Immunoprecipitates were washed 4 times with HES lysis buffer and resuspended in 30 μL Laemmli sample buffer. After boiling at 100°C for 10 minutes, bound proteins released from the beads were separated on 7% SDS-PAGE and transferred to polyvinylidene difluoride membrane followed by immunoblot analysis with anti-IRS-1 antibody and anti-IRβ antibody. The intensity of ECL signals in the linear range was quantitated by densitometric analysis. Results are expressed as amounts of IRS-1 bound to IR-β subunit in insulin-treated preparations after subtraction of binding in the basal state. Results are the mean ± SEM of 10 different pools of liver homogenates from HCV and 3 separate pools of non-HCV-infected subjects. *$P < .05$ versus non-HCV.

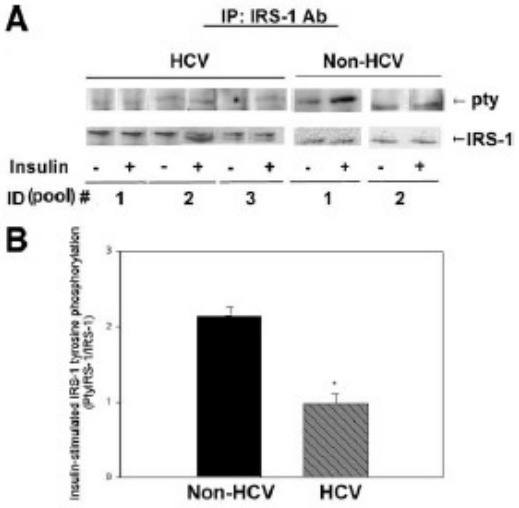


Fig. 5. HCV infection results in impaired insulin-stimulated IRS-1 tyrosine phosphorylation in liver. Pools of liver homogenates with equal amounts of proteins (4 mg) were immunoprecipitated with IRS-1 antibody (8 μg) as detailed in the legend to Fig. 4. The immunoprecipitates were washed and proteins separated on 7% SDS-PAGE followed by immunoblot analysis with anti-phosphotyrosine antibody. Blots were stripped and reprobed with anti-IRS-1 antibody. (A) A representative Western blot. (B) Quantitative analysis of insulin-stimulated IRS-1 tyrosine phosphorylation by densitometric scanning. Results are the mean ± SEM of 10 different pools of liver homogenates from HCV-infected subjects and 3 non-HCV-infected subjects. *$P < .005$ versus non-HCV.

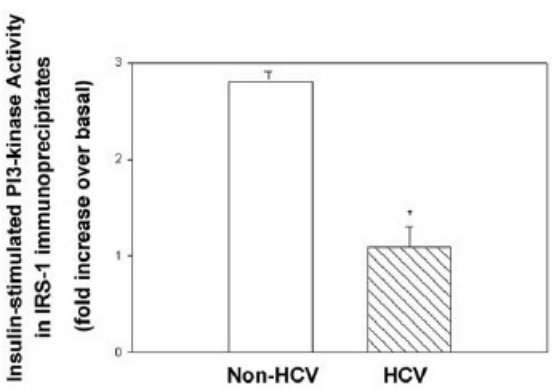


Fig. 7. HCV infection results in impaired activation of IRS-1–associated PI3-kinase activity. Individual homogenate proteins (500 μg) extracted from untreated and insulin-treated liver biopsy specimens obtained from HCV-infected and non-HCV-infected subjects were immunoprecipitated with IRS-1 antibody (1 μg). After extensive washing, PI3-kinase activity in the immunoprecipitates was assayed using phosphatidylinositol as a substrate in the presence of γ[^{32}P]-adenosine triphosphate as detailed in Materials and Methods. At the end of the reaction, lipids were extracted with chloroform methanol, dried under N_2, and separated by thin-layer chromatography followed by autoradiography. PIP spots were identified using standard phosphatidyl inositol phosphate, scraped, and radioactivity counted. Results are mean ± SEM of 10 HCV and 10 non-HCV liver samples. *$P < .005$ versus non-HCV.

Ridotta formazione e fosforilazione di IR-IRS 1. Ridotta attivazione della PI3-K

Impaired IRS-1/PI3-Kinase Signaling in Patients With HCV: A Mechanism for Increased Prevalence of Type 2 Diabetes

Serhat Aytug,[1] David Reich,[2] Lawrence E. Sapiro,[1,3] David Bernstein,[4] and Najma Begum[1,3]

HEPATOLOGY, Vol. 38, No. 6, 2003

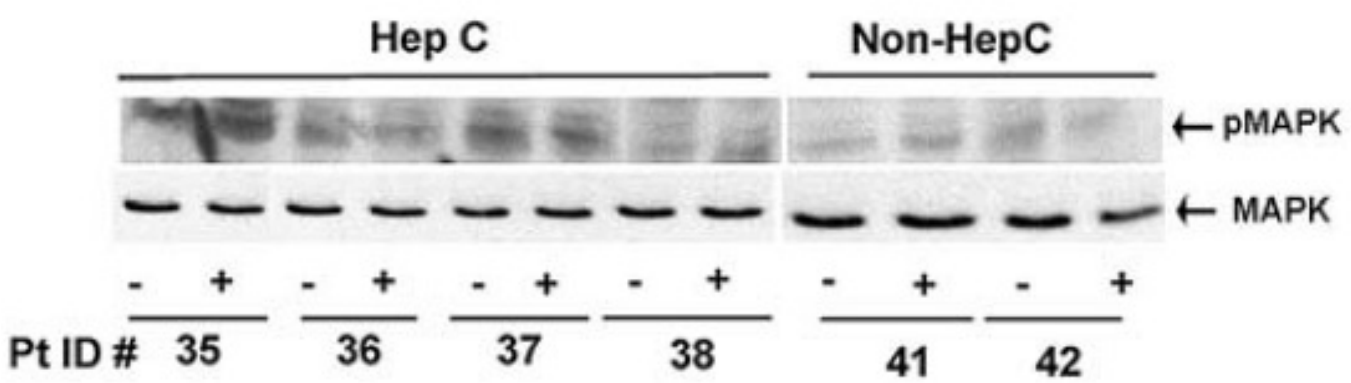


Fig. 9. HCV results in elevated MAPK phosphorylation in the liver. Equal amounts of liver homogenate proteins (100 μg) from Fig. 1 were subjected to 10% SDS-PAGE followed by immunoblot analysis with pMAPK antibodies. A representative Western blot is shown. Similar results were obtained in other samples.

Aumento della fosforilazione della MAPK

Diabete e HIV

- La prevalenza stimata di insulino-resistenza, alterata tolleranza glucidica e diabete mellito è compresa tra 4.5 e 12% dei casi di HIV
- L'iperglicemia è presente nel 3-10% dei soggetti in terapia antiretrovirale

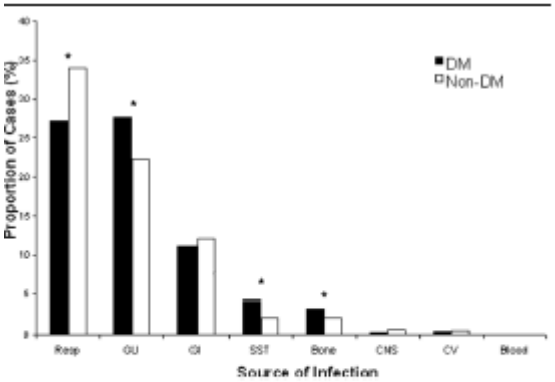
Diabete e HIV

Diabete dovuto a infezione da HIV	Diabete come risultato di fattori iatrogeni
Fattori di rischio (età, sesso, BMI, gruppo etnico)	Terapia anti-retrovirale :
Distruzione autoimmune	insulino-resistenza
Co-infezione da HCV	ridotta secrezione insulinica
Fattori infiammatori	elevati livelli di molecole pro-infiammatorie : PCR, TNF, IL6
Fattori virali	lipodistrofia
Basse concentrazioni di CD4	lipotossicità
Durata dell'infezione	

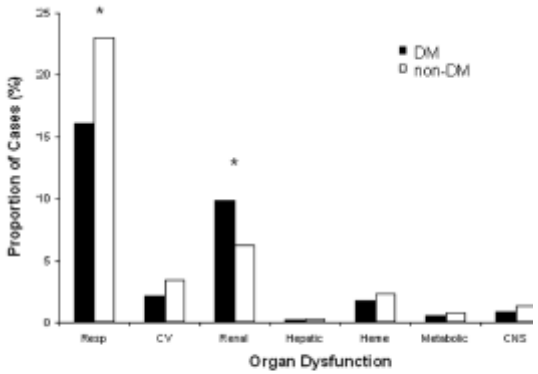
The effect of diabetes mellitus on organ dysfunction with sepsis: an epidemiological study

Annette M Esper[1], Marc Moss[2] and Greg S Martin[1]

Critical Care 2009, **13**:R18 (doi:10.1186/cc7717)



requency of sepsis cases. Frequency of sepsis cases among patients with diabetes mellitus (DM) and those with no diabetes mellitus (non-DM) with a source of infection identified.
CV = cardiovascular; GI = gastrointestinal; GU = genitourinal; Resp =



Frequency of acute organ dysfunction. Frequency of acute organ dy function in patients with diabetes mellitus (DM) and those with no di betes mellitus (non-DM) with a respiratory source of sepsis.
CV = cardiovascular; Heme = haematological; Resp = respiratory. * < 0.05.

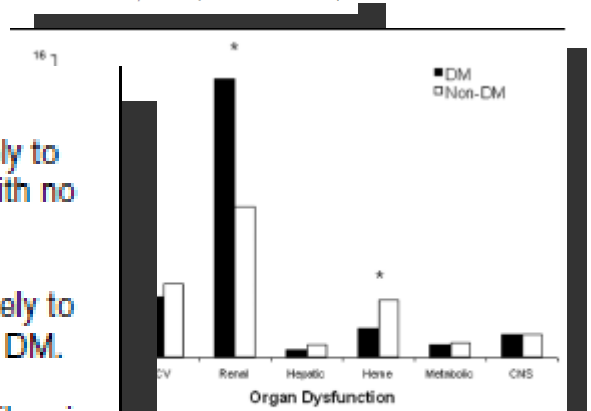
Key messages

- Patients with DM and severe sepsis are less likely to develop acute respiratory failure than patients with no DM, irrespective of source of infection.
- Patients with DM and severe sepsis are more likely to develop acute renal failure than patients with no DM.
- The decreased frequency of acute respiratory failure in patients with DM and severe sepsis did not translate into a significant difference in case fatality.

Diabetes and sepsis outcomes – it is not all bad news

Sachin Yende[1,2] and Tom van der Poll[3]

Critical Care 2009, **13**:117 (doi:10.1186/cc7707)



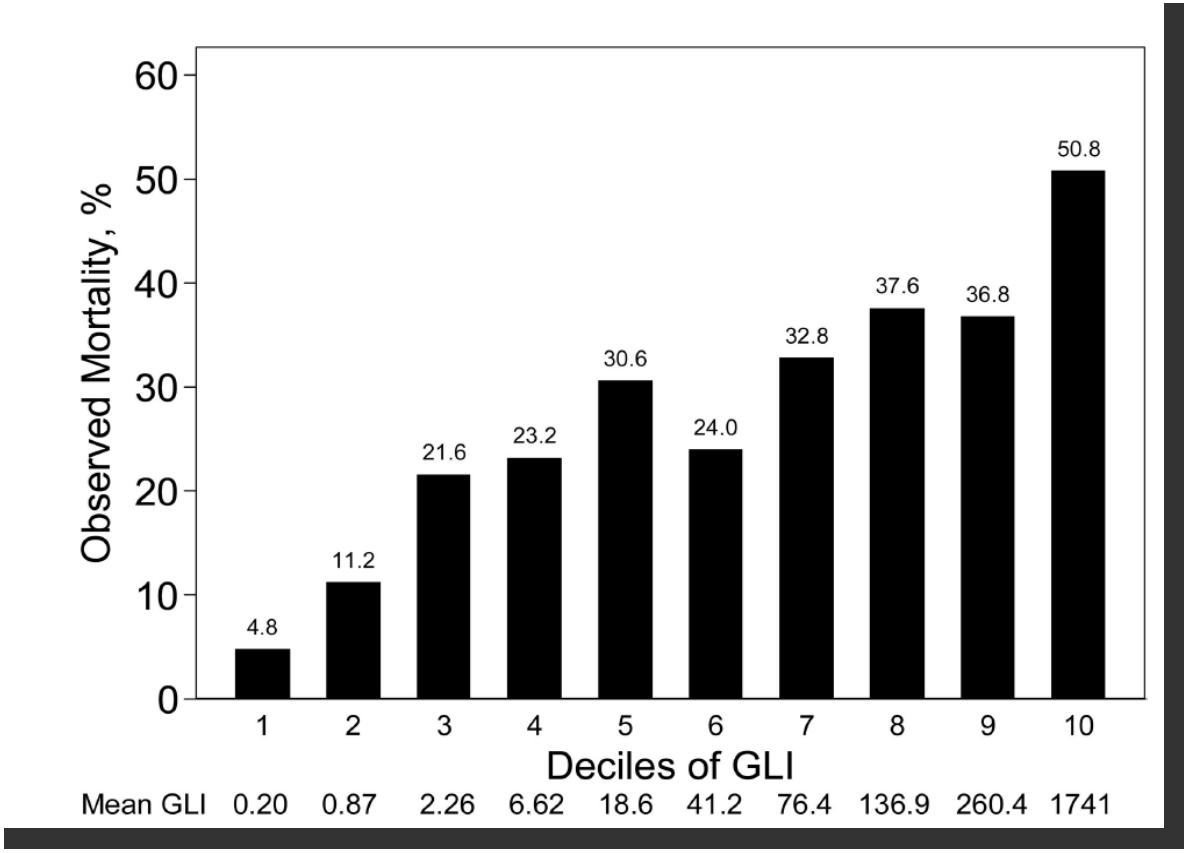
n dysfunction. Frequency of organ dysfunction in tes mellitus (DM) and those with no diabetes melli- a non-respiratory source of sepsis.
ar; Heme = haematological; Resp = respiratory. * p

XIX CONGRESSO NAZIONALE AMD
Roma, 29 maggio - 1 giugno 2013
Rome Marriott Park Hotel

Glucose variability and mortality in patients with sepsis*

Naeem A. Ali, MD; James M. O'Brien Jr, MD, MSc; Kathleen Dungan, MD; Gary Phillips, MAS; Clay B. Marsh, MD; Stanley Lemeshow, PhD; Alfred F. Connors Jr, MD; Jean-Charles Preiser, MD, PhD

Crit Care Med. 2008 August ; 36(8): 2316–2321.



Conclusioni

- I soggetti diabetici presentano un rischio infettivo aumentato
- Le infezioni tendono ad avere decorso ed outcomes peggiori. In particolare i dati suggeriscono, nel diabetico, peggiori outcomes nelle infezioni polmonari e delle vie urinarie e minor rischio di ARDS in corso di sepsi
- Alla luce di decorso ed outcomes delle infezioni i trattamenti antibiotici devono essere più aggressivi e prolungati .

AOU "Maggiore della Carità" – Novara
Mal. Metaboliche – Diabetologia e Endocrinologia

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