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25TH YEAR OF PUBLICATION

This document is divided into two parts

1) The **HIGHLIGHTS AND *EDITORIAL COMMENTS* SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

EDITORIAL COMMENTS *are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 25-year publication of Practical Pointers.*

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 10 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.
Editor/Publisher.

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HIGHLIGHTS AND *EDITORIAL COMMENTS* AUGUST 2010

"Increased WC Was Associated With Higher Risk Of Mortality Independent Of BMI."

8-1 WAIST CIRCUMFERENCE AND ALL-CAUSE MORTALITY IN A LARGE U.S. COHORT

A large waist circumference (**WC**) is associated, independent of BMI, with higher circulating levels of inflammatory markers, insulin resistance, diabetes, dyslipidemia, and coronary heart disease. This may be because WC is strongly correlated with visceral adipose tissue, which is more pathogenic than subcutaneous adipose tissue.

This study focused on examining associations of high levels of WC (> 88 cm in women and >102 cm in men; 35" and 40") within standard categories of BMI. Quantifying these risks is important because more than 50% of men and 70% of women in the US between ages 50-70 now exceed the WC threshold for abdominal obesity.

Participants in this analysis were drawn from participants in the Cancer Prevention Study II cohort established in 1992. At enrollment (1992 - 1993) participants (mean age 68) completed a 10-page self-administered health questionnaire. WC was first ascertained in 1997. Participants were provided with a tape measure and asked to measure their WC just above their navel to the nearest quarter inch while standing.

Calculated the BMI from weight reported in 1997 and height reported in 1992. After exclusions, a total of 48 500 men and 56 343 women remained for analysis. Recorded deaths from 1997 to 2006.

Relative risks of mortality (**RR**) gradually increased, approximately linearly, as WC increased by 5 cm increments.

RRs of all cause mortality by WC within categories of BMI:

	BMI 18.5-24.9 (normal)	BMI 25 to 29.9 (overweight)	BMI 30 and higher (obese)
WC (cm)			
Men			
< 90	1.00 (reference)	1.00	--
90-109	1.14	1,06	1.00
100 to 110	1.41	1.21	1.38
>110	--	1.50	1.69
Women			
<75	1.00 (reference)	--	--
75-84	1.24	1.00	

85-94	1.52	1.21	1.00
95-104	2,04	1.40	0.94
105 & higher	--	1.77	1.27

(-- not calculated)

In women, higher levels of WC were more strongly associated with mortality among those with normal BMI than among women who were overweight and obese. Among men, the association between WC and mortality did not vary significantly with BMI.

. "In this large prospective cohort, increased WC was associated with higher risk of mortality independent of BMI."

WC was positively associated with risk of mortality among individuals within all categories of BMI examined (normal, overweight, and obese). The RRs associated with a 10-cm increase ranged from approximately 15% to 25% within various categories of BMI.

This study emphasizes the importance of WC as a risk factor for mortality in older adults regardless of whether BMI is categorized as normal, overweight, or obese.

It *may be more impressive to the patients if the abdominal circumference were measured, and the excess girth categorized in inches, and compared with normal. However, primary care clinicians need only eye-ball the abdomen to determine the problem, which is indeed ubiquitous.*

Intra-peritoneal fat is metabolically active because it drains directly into the liver leading to non-alcoholic hepatic liver disease. Extra-peritoneal abdominal fat is less metabolically active. It drains into the general circulation.

Risk of cardiovascular disease is increased in patients with non-alcoholic fatty liver disease in proportion to the degree of steatosis. (NEJM September 30, 2010; 363: 1341-50)

"Only 13% Of The Cohort Maintained Normal Lipid Levels Throughout Young Adulthood"

8-2 NON-OPTIMAL LIPIDS COMMONLY PRESENT IN YOUNG ADULTS AND CORONARY CALCIUM LATER IN LIFE

This study evaluated the atherosclerotic consequence of lipid abnormalities during young adulthood.

It is not clear whether cholesterol levels are important earlier in life when short-term risk of CHD is low. Whether early-life lipid levels can cause atherosclerotic damage during young adulthood that persists into middle age is not known.

This prospective cohort study used repeated measurement of fasting lipids, beginning at onset of adulthood and continuing over 20 years of follow-up.

Recruited healthy volunteers (n = 3258) in 4 US cities in 1985-86. Consenting participants underwent baseline examination and repeated follow-up emanations periodically up to 20 years.

Calculated the average lipid levels to estimate the cumulative exposure to each lipid from age 20 to 35. Categorized average exposure for each lipid as normal, borderline, or abnormal according to The National Cholesterol Education Program guidelines.

At year 15 and year 20 all underwent a computed tomography of the coronary arteries to determine calcium content.

Defined lipid levels (mg/dL)	Optimal	Non-optimal	
	Normal	Borderline	Abnormal
LDL-c	<100	100-159	160 & over
HDL-c	60 and over	40-59	39 and under
Triglycerides	<150	150-199	200 and over

Average age at time of coronary calcium score = 45

Average exposure to lipids before age 35 and coronary calcium:

	Participants	% with calcium
Overall	3258	17
Lipid exposure category*		
Normal	434	7
Borderline	2443	17
Abnormal	381	30
Time averaged LDL-c		
<70	116	8
160 and over	123	44
Time averaged HDL-c		
> 70	296	13
< 40	293	26
Time averaged TG		
< 50	592	10
200 and over	24	38

(* Categorized according to their most abnormal lipid level.)

Only 13% of the entire cohort maintained normal lipid levels throughout young adulthood.

Abnormal levels were associated with: male sex; white race; higher income; family history of

premature CHD; low levels of self-reported physical activity; diabetes, alcohol consumption; high BMI; high waist circumference; and higher BP.

"Our results suggest that atherosclerotic changes begin during young adulthood as a result of commonly observed non-optimal lipid levels, that these changes persist into middle age, and that maintaining optimal levels of lipids (particularly LDL-cholesterol) throughout young adulthood could provide substantial benefits in terms of CHD prevention,."

Even moderately elevated lipid levels seen in most young adults were associated with coronary calcium later in life.

"Moderate elevations of LDL cholesterol and other lipids are commonly ignored by both patients and physicians during young adulthood."

These findings reinforce the importance of a heart-healthy diet exercise, and maintenance of normal weight beginning in young adulthood.

This is an important application for primary care and public health. I believe these concerns can be extended to adolescence and even childhood. Atherosclerosis begins at an early age and progresses over the lifetime. Coronary calcium indicates an advanced stage of atherosclerosis.

I would check lipid profiles in the young rarely. However, in extreme circumstances, it might be reasonable. We can easily gauge risk by a number of other factors.

Even more rarely would drug therapy in the young be applicable.

Delaying or preventing its gradual development in early age carries a legacy effect into middle age. Lower risk in middle age is related to reduced risk later in life.

To Have A Meaningful Effect, PC Services Must Be Provided Early In The Course Of The Disease

8-3 EARLY PALLIATIVE CARE FOR PATIENTS WITH METASTATIC NON-SMALL-CELL LUNG CANCER

Palliative care (**PC**) , with its focus on management of symptoms, psychosocial support, and assistance with decision making, has the potential to improve the quality of care and reduce the use of medical services. However, PC has traditionally been delivered late in the course of disease for patients with uncontrolled symptoms. Late referral to PC is inadequate to alter the quality and delivery of care provided for patients with cancer.

The goal of this study was to examine the effect of early palliative care (**EPC**) integrated with standard oncologic care on patient-reported outcomes, use of health services, and quality of end-of-life care among patients with terminal cancer.

Enrolled ambulatory patients with newly diagnosed metastatic lung cancer between 2006 and 2009 in a non-blinded randomized trial of 1) EPC integrated with standard oncologic care vs 2) standard oncologic care alone. Patients were enrolled within 8 weeks of diagnosis.

Guidelines from the National Consensus Project for Quality Palliative Care were included in the study protocol. Significant attention was paid to assessing physical and psychosocial symptoms, establishing goals of care, assisting with decision making regarding treatment, and coordinating care on the basis of the individual needs of the patient.

Health care quality of life was measured by several scales which assessed multiple dimensions of quality-of-life (physical, functional, emotional, and social well-being), and seven symptoms specific to lung cancer.

Early integration of PC resulted in longer survival (about 2 months), and clinically meaningful improvements in quality of life and mood. Rates of depression were lower in the EPC group by about half. EPC was also associated with greater documentation of preferences for resuscitation, an essential step in clarifying and ensuring respect of patient's wishes.

EPC also led to less aggressive end-of-life care including reduced chemotherapy, and longer hospice care Integration of EPC with standard oncologic care may facilitate the optimal and appropriate administration of anticancer therapy. With earlier referral to hospice, patients may receive care that results in better management of symptoms, leading to prolonged survival.

The study was not able to assess the effect of diversity of race

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This study was much more complex than I have indicated.

The results apply to many primary care patients who are terminal, not necessarily from cancer.

I wonder if prolonging life by 2 months is a benefit. These patients, even if they were made more comfortable, must have continued to suffer without hope of cure, and be more dependent. Unless there were some pressing personal or family need, I doubt 2 more months of life would be a reasonable goal.

Note that the subjects in this study were outpatients. The fewer days spent in the hospital is a major achievement.

The author's comment about race is important. Some cultures require that "everything be done" and that life be prolonged as much as possible.

PC Is Appropriate When It Is Introduced At The Time of Diagnosis of A Serious Or Life-Threatening Illness.

8-4 PALLIATIVE CARE--A SHIFTING PARADIGM [Editorial]

Palliative care (**PC**) focuses on relieving suffering and achieving the best possible quality of life (**Q-O-L**) for patients and their caregivers. It involves the assessment and treatment of symptoms, support for decision-making, assistance in matching treatments to informed patient and family goals, practical aid of patients and their family caregivers, mobilization of community resources to ensure a secure and safe living environment, and collaborative and seamless models of care across a range of care settings (hospital, home, nursing home, and hospice).

Despite increasing availability of PC, and evidence showing the great distress of the illness, the burdens of caregivers, and the overuse of costly , ineffective therapies during advanced chronic illness, the use of PC by physicians and their patients remains low. Physicians tend to perceive PC as the alternative to life-prolonging or curative care--what we do when there is nothing more that we can do--rather than a simultaneously delivered adjunct to the disease-focused treatment.

PC is appropriate and potentially beneficial when it is introduced at the time of diagnosis of a serious of life-threatening illness. PC can improve quality-of life outcomes.

The Charlotte, North Carolina region is blessed with a well-organized hospice and palliative care organization. I wish it had been available when I was in active practice.

I agree that the chief obstacle to proper use of PC is delayed calls for assistance.

Support for families of seriously ill patients is an important responsibility of PC.

In 2005-06, 1 In 5 US Adolescents Demonstrated Hearing Loss

8-5 CHANGE IN PREVALENCE OF HEARING LOSS IN US ADOLESCENTS

Hearing loss (**HL**) is a common sensory disorder of millions of individuals in the US. In school-aged children, even slight HL (15-24 dB) can create a need for speech therapy and auditory training. Mild HL in young children can impair speech and language development and decrease educational and social-emotional development.

This study of 12 to 19 year old subjects, compared their health status in The Third National Health and Nutrition Examination Survey (NHANES 1988-94) with NHANES 2005-06. Conducted meticulous audiometry in both groups. Defined HL as low or high frequency loss greater than 15 dB in either ear.

Hearing loss prevalence	NHANES 1989-94 (n = 2928)	NHANES 2005-06 (n = 1771)
Any HL (%)		
> 15 dB	14.9	19.5
15 - 24 dB	11.4	14.2

> 25 dB	3.5	5.3
Bilateral HL (%)		
> 15 dB	3.8	5.5
15 - 24 dB	2.9	4.7
> 25 dB	0.8	0.8

The prevalence of HL increased by 31% over this time. The prevalence of high frequency HL was higher in 2005-06. The prevalence of low frequency HL did not differ. Males were more likely to have any HL than females.

In 2005-06, 1 in 5 US adolescents demonstrated HL. This represents a 1/3 increase in the prevalence of HL over 10+ years. Most HL was slight. Most HL was unilateral. High frequency HL was more common.

However, the prevalence of HL of 25 dB or greater increased from 3.5% to 5.3%, indicating that one in 20 had mild or worse HL

The reason for the increasing loss is not known. Untreated middle ear disease is not likely to explain the HL. The study did not find a difference in estimated noise exposure between the 2 time periods.

Conclusion: Prevalence of HL among a sample of US adolescents age 12 to 19 was greater in 2005-06 than 1988-94.

Is there an application for primary care here? I believe there is.

Repeated exposure to loud noise does cause hearing loss. Avoiding excess noise is part of a healthy lifestyle, which primary care clinicians constantly advise. So, protect your ears!

Exposure to noise is ubiquitous and growing. Lawn and industrial machinery, traffic, crowds at sports events, and adolescent music are very loud, including the notorious "boom box".

Avoids The Twin Hazards Of Hypoglycemia And Weight Gain

8-6 EFFICACY AND SAFETY OF EXENATIDE ONCE WEEKLY VERSUS SITAGLIPTIN OR PIOGLITAZONE AS AN ADJUNCT TO METFORMIN FOR TREATMENT OF TYPE-2 DIABETES

This randomized trial compared the efficacy, safety, and tolerability of three recommended therapies (in addition to metformin) for patients not sufficiently controlled on metformin alone.

Recruited 514 patients in 2008 in 72 hospitals and clinics. All had type-2 diabetes (**DM-2**) but were otherwise healthy. All had been treated with a stable metformin regimen for at least 2 months.

Randomized to: 1) Exenitide 2 mg once weekly subcutaneous injection + oral placebo once daily, + metformin 2) Pioglitazone 45 mg orally once daily + placebo once weekly by injection, + metformin, or 3) Sitagliptin 100 mg orally + once weekly placebo injection + metformin. Stable doses of metformin were continued in all. Doses of sitagliptin and pioglitazone were considered maximum.

At 26 weeks, treatment with exenatide resulted in a greater reduction of HbA1c than sitagliptin. For pioglitazone, the difference was significant only in those with baseline HbA1c 9.0% and above.

Change in HbA1c was determined relative to 2 baseline levels: < 9.0% and 9.0% and above

A. HbA1c < 9.0%

	Exenatide (n = 102)	Sitagliptin (n = 106)	Pioglitazone (n = 109)
Baseline HbA1c	7.8%	7.7%	7.8%
Change in HbA1c	-1.1%	-0.5%	-0.9%
Treatment difference vs exenatide	NA	0.6%	0.2% (Not significant)

B. HbA1c 9.0% and above

	Exenatide (n = 58)	Sitagliptin (n = 60)	Pioglitazone (n = 56)
Baseline HbA1c	9.9%	9.8%	9.7%
Change in HbA1c	-2.0%	-1.3%	-1.5%
Treatment difference vs exenatide	NA	0.7%	0.5%

At 26 weeks, 60% of exenatide patients had HbA1c less than 7.0% and 35% had levels below 6.5%. Fasting blood glucose declined by 32 mg/dL. Fasting insulin levels rose.

In the exenatide group, there were small, but favorable changes in bodyweight, systolic BP, HDL-cholesterol, LDL-cholesterol, triglycerides, albumin / creatinine ratio, C-reactive protein, and quality of life.

Adverse effects of exenatide over 26 weeks: Nausea 23%; diarrhea 18%; vomiting 11%; fatigue 6%; and constipation 6%; 11 patients withdrew because of adverse effects.

There were no episodes of major hypoglycemia; two events of minor hypoglycemia.

"These data suggest that exenatide once weekly offers clinically meaningful improvements in patients not achieving adequate glycemic control on metformin alone."

Improvements in lipids and markers of cardiovascular risk were noted to varying degrees in all 3 treatments. Exenatide was the only drug associated with favorable mean changes in all the parameters.

Conclusion: Addition of exenatide once weekly to metformin achieved the goal of better glycemic control with weight loss and minimum hypoglycemia more often than did the addition of maximum doses of sitagliptin or pioglitazone.

Because this formulation of exenatide has not been approved by the FDA, this is not a practical point at this time I abstracted the article because of its apparent promise. If we can avoid hypoglycemia and weight gain, we may be able to more safely reduce BP and HbA1c levels.

Exenatide is an incretin mimetic. It increases insulin secretion after a meal, decreases glucagon secretion, delays stomach emptying, and increases satiety.

We await long-term studies about costs, safety, and effect on clinical outcomes.

Exenatide has been available as "Byetta" from Amylin Pharmaceuticals in a short-acting form given twice daily. The exenatide described in this article is long-acting. It is attached to a different type of microsphere, which delays absorption. Half-life is 2 weeks. A steady state is achieved in 6 weeks.

See Practical Pointers March 2010 [3-3] for more details about these drugs.

ABSTRACTS AUGUST 2010

"Increased WC Was Associated With Higher Risk Of Mortality Independent Of BMI."

8-1 **WAIST CIRCUMFERENCE AND ALL-CAUSE MORTALITY IN A LARGE U.S. COHORT**

A large waist circumference (**WC**) is associated, independent of BMI, with higher circulating levels of inflammatory markers, insulin resistance, diabetes, dyslipidemia, and coronary heart disease. This may be because WC is strongly correlated with visceral adipose tissue, which is more pathogenic than subcutaneous adipose tissue.

Two important areas of uncertainty remain: 1) Risks have not been well quantified for very large WCs that substantially exceed the clinically defined thresholds for abdominal obesity (88 cm or larger for women; 102 cm or larger for men). Quantifying these risks is important because more than 50% of men and 70% of women in the US between ages 50-70 now exceed the WC threshold for abdominal obesity. 2) Few studies have examined the association between WC and mortality within categories of body mass index (**BMI**). Understanding how WC is associated with risk of mortality within normal, overweight, and obese categories of BMI may be useful in determining when measurement of WC could provide meaningful information beyond that provided by BMI .

This study focused on examining associations of high levels of WC within standard categories of BMI

STUDY

1. Men and women in this analysis were drawn from participants in the Cancer Prevention Study II cohort established in 1992.
2. At enrollment (1992 - 1993) participants completed a 10-page self-administered health questionnaire. WC was first ascertained in 1997 in a follow-up questionnaire, which also contained information on current weight, smoking, and other health-related factors. Participants were provided with a tape measure and asked to measure their WC just above their navel to the nearest quarter inch while standing.

3, Calculated the BMI from weight reported in 1997 and height reported in 1992.

4. After exclusions, a total of 48 500 men and 56 343 women remained for analysis.

5. Recorded deaths from 1997 to 2006.

RESULTS

1. Median age at baseline was 69 for men and 67 for women
2. Those in the highest category of WC were more likely than those with smaller waists to be less educated, to have higher BMI, to be physically inactive, to be former smokers, and to have a history of CVD, cancer, and respiratory disease.
3. All-cause mortality by WC 1997-2006

Men (WC in cm)	Multivariate and BMI-adjusted RR of death
< 90	1.00 (referent)
> 120	2.02
Women	
<75	1.00 (reference)
>110	2.36

(RR gradually increased, approximately linearly, as WC increased by 5 cm increments.)

4. A WC of 102 cm in men (the cut point for WC) and above, was associated with a RR of 1.17 of death compared with those with a WC less than 102. Among women with a WC of 88 cm and above, the RR of death was 1.23 compared with those with a WC of less than 88.
5. WC was positively associated with higher risk of mortality within all categories of BMI.
6. After adjustment for WC, high levels of BMI were no longer associated with increased risk of mortality.
7. Relative risk (**RR**) of all cause mortality by WC within categories of BMI:

	BMI 18.5-24.9 (normal)	BMI 25 to 29.9 (overweight)	BMI 30 and higher (obese)
WC (cm)			
Men			
< 90	1.00 (reference)	1.00	--
90-109	1.14	1,06	1.00
100 to 110	1.41	1.21	1.38
>110	--	1.50	1.69
Women			
<75	1.00 (reference)	--	--
75-84	1.24	1.00	
85-94	1.52	1.21	1.00
95-104	2,04	1.40	0.94

105 & higher	--	1.77	1.27

(-- not calculated)

7. In women, higher levels of WC were more strongly associated with mortality among those with normal BMI than among women who were overweight and obese. Among men, the association between WC and mortality did not vary significantly with BMI.
8. Among men, RRs associated with WC were lower among those younger than age 70 at baseline than those older than 70.
9. In men, the RR associated with WC of 110 cm compared with those with WC of 90 cm was 1.91.

DISCUSSION

1. "In this large prospective cohort, increased WC was associated with higher risk of mortality independent of BMI."
2. After adjustment for BMI, increasing levels of WC were associated with progressively higher risk of mortality in men and women.
3. "In our study, WC was positively associated with risk of mortality among individuals within all categories of BMI examined (normal, overweight, and obese). The relative risks (**RR**s) associated with a 10-cm increase ranged from approximately 15% to 25% within various categories of BMI."
4. In the large National Institute of Health cohort, individuals in the normal BMI category who were abdominally obese (> 88 cm for women; >102 cm for men; 35" and 40") were at approximately 20% higher risk than individuals with normal BMI who were not abdominal obese.
5. "A larger WC may have important adverse health effects even among individuals with BMI lower than 30."
6. The associations with WC were strongest for mortality caused by respiratory disease. This is consistent with the fact that a high WC is associated with considerably reduced respiratory function.
7. This study emphasizes the importance of WC as a risk factor for mortality in older adults regardless of whether BMI is categorized as normal, overweight, or obese.

CONCLUSION

"These results emphasize the importance of WC as a risk factor for mortality in older individuals, regardless of BMI."

Archives Internal Medicine August 9/23 2010; 170: 1293-1301 Original investigation by The Cancer Prevention Study II, firs author Eric J Jacobs, American Cancer Society, Atlanta, GA

Only 13% Of The Cohort Maintained Normal Lipid Levels Throughout Young Adulthood.

8-2 NON-OPTIMAL LIPIDS COMMONLY PRESENT IN YOUNG ADULTS AND CORONARY CALCIUM LATER IN LIFE

It is not clear whether cholesterol levels are important earlier in life when short-term risk of CHD is low. Whether early-life lipid levels can cause atherosclerotic damage during young adulthood that persists into middle age is not known.

This study evaluated the atherosclerotic consequence of lipid abnormalities during young adulthood.

STUDY

1. This prospective cohort study used repeated measurement of fasting lipids, beginning at onset of adulthood (age 18 to 30) and continuing over 20 years of follow-up.
2. Recruited healthy volunteers (n = 3258) in 4 US cities in 1985-86. Consenting participants underwent baseline examination and repeated follow-up emanations periodically up to 20 years.
3. Fasting lipid levels were drawn at each study examination.
4. Calculated the average lipid levels to estimate the cumulative exposure to each lipid from age 20 to 35. Categorized average exposure for each lipid as normal, borderline, or abnormal according to The National Cholesterol Education Program guidelines.
5. At year 15 and year 20 all underwent a computed tomography of the coronary arteries to determine calcium content.

RESULTS

1. Defined lipid levels (mg/dL)

	Optimal	Non-optimal	
	Normal	Borderline	Abnormal
LDL-c	<100	100-159	160 & over
HDL-c	60 and over	40-59	39 and under
Triglycerides	<150	150-199	200 and over

2.. Average age at time of coronary calcium score = 45

3. Average exposure to lipids before age 35 and coronary calcium:

	Participants	% with calcium
Overall	3258	17
Lipid exposure category*		
Normal	434	7
Borderline	2443	17

Abnormal	381	30
Time averaged LDL-c		
<70	116	8
160 and over	123	44
Time averaged HDL-c		
> 70	296	13
< 40	293	26
Time averaged TG		
< 50	592	10
200 and over	24	38

(* Categorized according to their most abnormal lipid level.)

4. Only 13% of the entire cohort maintained normal lipid levels throughout young adulthood. 12% had at least one abnormal level. The remaining 75% had non-optimal levels.
5. LDL-c levels during young adulthood remained strongly associated with coronary calcium later in life. HDL-c and TG had weaker associations that were not statistically significant after adjustment analysis.
6. Abnormal levels were associated with: male sex; white race; higher income; family history of premature CHD; low levels of self-reported physical activity; alcohol consumption; high BMI; high waist circumference; and higher BP.
7 Lipid levels during young adulthood were strongly associated with lipid exposure before age 35; 44% of those with a LDL-c of 160 or greater had coronary calcium compared with 8% of those with levels less than 70.

DISCUSSION

1. Non-optimal LDL-c levels during young adulthood were associated with coronary calcification later in life.
2. “Our results suggest that atherosclerotic changes begin during young adulthood as a result of commonly observed non-optimal lipid levels, that these changes persist into middle age, and that maintaining optimal levels of lipids (particularly LDL-cholesterol) throughout young adulthood could provide substantial benefits in terms of CHD prevention,.”
3. Other studies of children and young adults show associations between lipid levels and atherosclerosis, demonstrated by autopsy and carotid intima-media.
4. Even moderately elevated lipid levels seen in most young adults were associated with coronary

calcium later in life.

5. Participants who maintained LDL-c below 70 during young adulthood without lipid-lowering medication had a very low prevalence of coronary calcium in middle life.
6. “Moderate elevations of LDL cholesterol and other lipids are commonly ignored by both patients and physicians during young adulthood.”
7. “The strong clinical evidence that LDL cholesterol-lowering agents reduce CHD incidence and mortality leaves little doubt about the causal basis for the association between LDL-cholesterol and CHD.”
8. Some of the atherosclerotic changes that occur during young adulthood may be preventable with optimization of LDL-c and HDL-c.
9. “We relied on a subclinical end point (coronary calcium score) because our cohort is still too young to have had many myocardial infarctions or deaths from CHD; however, coronary calcium is a strong independent predictor of CHD events, and the absence of coronary calcium is a strongly protective factor.”
10. These findings reinforce the importance of a heart-healthy diet, exercise, and maintenance of normal weight beginning in young adulthood.
11. Whether to screen and treat younger patients for suboptimal lipid levels before middle age is less clear. Meanwhile young adults should realize that what they eat and now much they exercise is important even in younger life, even when short term risk is extremely low.

CONCLUSION

Non-optimal levels of LDL-c and HDLc during young adulthood are independently associated with coronary atherosclerosis 2 decades later.

Annals Internal Medicine August 5, 2010; 153: 137-146 Original investigation by the CARDIA study, “Coronary Artery Risk Development In young Adults” first author Mark J Pletcher, University of California, San Francisco. Sponsored by the National Heart, Lung and Blood Institute.

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To Have A Meaningful Effect, PC Services Must Be Provided Early In The Course Of The Disease

8-3 EARLY PALLIATIVE CARE FOR PATIENTS WITH METASTATIC NON-SMALL-CELL LUNG CANCER

The quality of care and the use of medical services for seriously ill patients at the end of life are key elements in the ongoing debate over reform of the US health care system. Oncologic care is central to this debate, largely because anticancer treatments are often invasive and costly.

Palliative care (**PC**) , with its focus on management of symptoms, psychosocial support, and assistance with decision making, has the potential to improve the quality of care and reduce the use of medical services. However, PC has traditionally been delivered late in the course of disease for patients with uncontrolled symptoms. Late referral to PC is inadequate to alter the quality and delivery of care provided for patients with cancer.

To have a meaningful effect on quality of life and end-of-life care, PC services must be provided early in the course of the disease. (Early PC [**EPC**])

Metastatic non-small-cell cancer (**MNSCLC**) of the lung, is the leading cause of death from cancer worldwide. It is debilitating, and results in a high burden of symptoms and poor quality of life. The estimated prognosis after diagnosis is less than one year. Introducing PC shortly after diagnosis is feasible and acceptable among outpatients with MNSCLC.

The goal of this study was to examine the effect of EPC integrated with standard oncologic care on patient-reported outcomes, use of health services, and quality of end-of-life care among patients with MNSCLC.

STUDY

1. Enrolled ambulatory patients with newly diagnosed MNSCLC between 2006 and 2009 in a non-blinded randomized trial of 1) EPC integrated with standard oncologic care vs 2) standard oncologic care alone. Patients were enrolled within 8 weeks of diagnosis.
2. Patients assigned to EPC met with a palliative care physician and advanced-care nurses within 3 weeks and monthly thereafter in the outpatient setting. Additional visits were scheduled as needed and requested.
3. Guidelines from the National Consensus Project for Quality Palliative Care were included in the study protocol. Significant attention was paid to assessing physical and psychosocial symptoms, establishing goals of care, assisting with decision making regarding treatment, and coordinating care on the basis of the individual needs of the patient.
4. Patients assigned to standard care were not scheduled to meet with palliative care services

unless a meeting was requested. Those who were referred did not cross over to the palliative group or follow the specific PC protocol. All continued to receive standard oncologic care.

5. Health care quality of life was measured by several scales[1], which assessed multiple dimensions of quality-of-life (physical, functional, emotional, and social well-being), and seven symptoms specific to lung cancer.
6. Mood was assessed with the use of 2 scales, including symptoms of anxiety and depression. Symptoms had to be present for more than half the time, except for suicidal thoughts, which was included in the diagnosis if it was present at any time.
7. Also collected data on use of hospital services, and end-of-life care, including anticancer therapy, medication, referral to hospice, hospital admissions, and date and location of death.
8. Primary outcome = change from baseline to 12 weeks in the score of the Trial Outcome Index, which is the sum of the scores of symptoms of lung cancer, and physical and functional well-being.

RESULTS

1. At baseline, 74 patients were assigned to standard care; 77 to early palliative care (mean age 65).
2. Patients assigned to PC had at least one visit with the palliative care service by the 12th week.
3. Differences in quality-of-life and mood outcomes at 12 weeks:

	Standard care	EPC	Difference
FACT-L	91.5	98.0	+6.5
LCS	19.1	21,0	+1.7 (Not statistically significant)
TOI	53.0	59.0	+6.0

4. End-of life care:
   1) A greater percentage of patients in the group assigned to standard care than those in the EPC group received aggressive end-of-life care. (54% vs 33%)
   2) Fewer patients in the standard care group than in the EPC group had resuscitation preferences documented. (28% vs 53%)
   3) EPC patients received more days of hospice care, fewer days of hospitalization, and fewer emergency department visits
   4) The EPC group had significantly longer survival. (11.6 months vs 8.9 months) despite receiving less aggressive end-of-life care,

DISCUSSION

1. Early integration of PC resulted in longer survival (about 2 months), clinically meaningful

improvements in quality of life and mood, and less aggressive care at the end of life. Rates of depression were lower in the EPC group by about half.

2. EPC was also associated with greater documentation of preferences for resuscitation, an essential step in clarifying and ensuring respect of patient's wishes.
3. EPC also led to less aggressive end-of-life care including reduced chemotherapy, and longer hospice care.
4. Integration of EPC with standard oncologic care may facilitate the optimal and appropriate administration of anticancer therapy.
5. With earlier referral to hospice, patients may receive care that results in better management of symptoms, leading to prolonged survival.
6. The improved quality of life in the EPC group occurred despite similar anti-cancer therapy.
7. "Our study also showed the early outpatient palliative care for patients with advanced cancer can alter the use of health care services, including care at end of life."
8. The study was not able to assess the effect of diversity of race.

CONCLUSION

Early palliative care led to significant improvements in both quality of life and mood. Patients receiving EPC had less aggressive care at the end of life, but longer survival.

NEJM August 18, 2010; 363:733-42. Original investigation, first author Jennifer S Temel, Massachusetts General Hospital, Boston.

1 FACT-L Functional Assessment of Cancer Therapy [0 to 136; higher score better Q-O-L]
Assesses multiple dimensions of quality of life (physical, functional, emotional, and social well being).

LCS The Lung Cancer Subscale [0 to 28; higher score fewer symptoms]
7 symptoms specific to lung cancer.

TOI The Trial Outcome Index [0-to 84. higher score better Q-O-L]
The sum of scores on the scores on the LCS and the physical and functional well-being subscales of FACT-L

HAD & PHQ-9
Hospital Anxiety and Depression Scale screens for anxiety and depression, and the Patient Health Questionnaire-9 measure symptoms of major depression.

PC Is Appropriate When It Is Introduced At The Time of Diagnosis of A Serious Or Life-Threatening Illness.

8-4 PALLIATIVE CARE--A SHIFTING PARADIGM

(This editorial comments and expands on the preceding article.)

Palliative care (**PC**) focuses on relieving suffering and achieving the best possible quality of life (**Q-O-L**) for patients and their caregivers. It involves the assessment and treatment of symptoms, support for decision-making, assistance in matching treatments to informed patient and family goals, practical aid of patients and their family caregivers, mobilization of community resources to ensure a secure and safe living environment, and collaborative and seamless models of care across a range of care settings (hospital, home, nursing home, and hospice).

PC is provided both within the Medicare hospice benefit, (hospice PC) and outside it (non-hospice PC). Non-hospice PC is offered simultaneously with life-prolonging and curative therapies for patients living with serious, complex, and life-threatening illness. Hospice PC becomes appropriate when curative treatments are no longer beneficial, when the burdens of treatments exceed their benefits, and when patients are entering the last weeks to months of life.

Comprehensive PC services integrate the expertise of a team of providers from different disciplines to address the complex needs of seriously ill patients and their families. Members of a PC team typically include professionals from medicine, nursing, social work, with additional support from chaplaincy, and professionals in nutrition, rehabilitation, pharmacy.

Despite increasing availability of PC, and evidence showing the great distress of the illness, the burdens of caregivers, and the overuse of costly, ineffective therapies during advanced chronic illness, the use of PC by physicians and their patients remains low. Physicians tend to perceive PC as the alternative to life-prolonging or curative care--what we do when there is nothing more that we can do--rather than a simultaneously delivered adjunct to the disease-focused treatment.

PC is appropriate and potentially beneficial when it is introduced at the time of diagnosis of a serious or life-threatening illness. PC can improve quality-of life outcomes.

NEJM August 19, 2010; 363:781-82 Editorial, first author Amy S Kelley, Mt Sinai School of Medicine, New York

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In 2005-06, 1 In 5 US Adolescents Demonstrated Hearing Loss

8-5 CHANGE IN PREVALENCE OF HEARING LOSS IN US ADOLESCENTS

Hearing loss (**HL**) is a common sensory disorder of millions of individuals in the US. In school-aged children, even slight HL (15-24 dB) can create a need for speech therapy and auditory training. Mild HL in young children can impair speech and language development and decrease educational and social-emotional development.

Some HL in children and adolescents can be attributed to identifiable causes (eg, infection, genetic syndromes, head trauma). Limited data exist on potential risk factors for much of acquired HL in this population. Adolescent HL, in particular, is not well understood.

Some risk factors, such as loud sound exposure from music listening may be important.

This study of 12 to 19 year old subjects, compared their health status in The Third National Health and Nutrition Examination Survey (NHANES 1988-94) with NHANES 2005-06. Conducted meticulous audiometry in both groups. Defined HL as low or high frequency loss greater than 15 dB in either ear.

Asked subjects if they had ever been exposed to steady loud noise or music for more than 5 hours peer week.

RESULTS

1. Hearing loss prevalence	NHANES 1989-94 (n = 2928)	NHANES 2005-06 (n = 1771)
Any HL (%)		
> 15 dB	14.9	19.5
15 - 24 dB	11.4	14.2
> 25 dB	3.5	5.3
Bilateral HL (%)		
> 15 dB	3.8	5.5
15 - 24 dB	2.9	4.7
> 25 dB	0.8	0.8

2. The prevalence of HL increased by 31% over this time. The prevalence of high frequency HL was higher in 2005-06. The prevalence of low frequency HL did not differ.
3. Males were more likely to have some HL than females.

DISCUSSION

1. In 2005-06, 1 in 5 US adolescents demonstrated HL. This represents a 1/3 increase in the

prevalence of HL Most HL was slight. Most HL was unilateral. High frequency HL was more common.

2. However, the prevalence of HL of 25 dB or greater increased from 3.5% to 5.3%, indicating that one in 20 had mild or worse HL
3. The reason for the increasing loss is not known. Untreated middle ear disease is not likely to explain the HL The study did not find a difference in estimated noise exposure between the 2 time periods.
4. However, adolescents typically underestimate the symptoms of loud sound---tinnitus and temporary HL during music exposure---and underreport concern for these conditions. Possibly, the finding of a significant increase in high-frequency HL between the 2 periods may indicate an increase in noise-induced HL.
5. Individuals from families below the federal poverty threshold had significantly higher odds of HL (OR = 1.60).
6. A recent cross-sectional study of children in Australia reported that use of personal stereo devices was associated with a 70% increase in risk of HL.
7. We need to determine reasons for the increase and to identify potential modifiable risk factors to prevent development of HL

CONCLUSION

Prevalence of HL among a sample of US adolescents age 12 to 19 was greater in 2005-06 than 1988-94.

JAMA August 18, 2010; 304: 772-78 Original investigation, first author Josef Shargorodsky, Channing Laboratory, Brigham and Women's Hospital, Boston, Mass

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Avoids The Twin Hazards Of Hypoglycemia And Weight Gain

8-6 EFFICACY AND SAFETY OF EXENATIDE ONCE WEEKLY VERSUS SITAGLIPTIN OR PIOGLITAZONE AS AN ADJUNCT TO METFORMIN FOR TREATMENT OF TYPE-2 DIABETES

The American College of Endocrinology now places metformin at the cornerstone of combination therapy for type-2 diabetes (**DM-2**), but also includes new classes of drugs to consider after metformin, with an emphasis on keeping hypoglycemia and weight gain to a minimum.

These new treatments include incretin mimetics [glucagon-like peptide receptor agonists (**GLP)**, eg. exenatide] and dipeptidyl peptidase inhibitors [eg. sitagliptin], which block the enzyme that normally degrades incretins. These new drugs could positively affect obesity, hyperlipidemia, and hypoglycemia.

Now, only 1 in 8 patients with DM-2 in the USA reaches the referenced targets for HbA1c, BP, and LDL-cholesterol.

This randomized trial compared the efficacy, safety, and tolerability of three recommended therapies (in addition to metformin) for patients not sufficiently controlled on metformin alone.

STUDY

1. Recruited 514 patients in 2008 in 72 hospitals and clinics in the US, Mexico, and India. All had DM-2, but were otherwise healthy, and had been treated with a stable metformin regimen for at least 2 months. HbA1c levels ranged from 7.1% to 11.0%, and BMI ranged from 25-45.
2. Randomized to: 1) Exenitide 2 mg once weekly subcutaneous injection + oral placebo once daily, + metformin 2) Pioglitazone 45 mg orally once dally + placebo once weekly by injection, + metformin, or 3) Sitagliptin 100 mg orally + once weekly placebo injection + metformin. Stable doses of metformin were continued in all. Doses of sitagliptin and pioglitazone were considered maximum.
3. Duration of study = 26 weeks. Primary endpoint was change in HbA1c from baseline to week 26. Analysis was by intention to treat.

RESULTS

1. Mean baseline characteristics were similar between groups:: Age 52; BMI 32; HbA1c 8.5%; fasting plasma glucose 164 mg/dL (9.1 mmol/L); duration of DM-2, 6 years; daily metformin 1520 mg.
2. At 26 weeks, treatment with exenatide resulted in a greater reduction of HbA1c than sitagliptin. For pioglitazone, the difference was significant only in those with baseline HbA1c 9.0% and above.
3. Change in HbA1c was determined relative to 2 baseline levels: < 9.0% and 9.0% and above

A. HbA1c < 9.0%

	Exenatide (n = 102)	Sitagliptin (n = 106)	Pioglitazone (n = 109)
Baseline HbA1c	7.8%	7.7%	7.8%
Change in HbA1c	-1.1%	-0.5%	-0.9%
Treatment difference vs exenatide	NA	0.6%	0.2% (Not significant)

B. HbA1c 9.0% and above

	Exenatide (n = 58)	Sitagliptin (n = 60)	Pioglitazone (n = 56)
Baseline HbA1c	9.9%	9.8%	9.7%
Change in HbA1c	-2.0%	-1.3%	-1.5%
Treatment difference vs exenatide	NA	0.7%	0.5%

4. All treatments improved fasting blood glucose. Exenatide was associated with a mean reduction of -32 mg/dL (1.8 mmol/L).
5. At 26 weeks, exenatide was associated with:

HbA1c levels <7.0% (60%) and below 6.5% (35%). [*My estimate from figure 2B. RTJ*)

Fasting insulin levels increased (+14uIU/mL). Levels associated with the other drugs remained the same or decreased

Body weight decreased in over 75%; 25% had weight loss of 5% or more

Systolic BP decreased by mean of 4 mm Hg,; decreased by 10 mm Hg in those with baseline systolic > 130

HDL-cholesterol increased slightly

LDL-cholesterol, total-cholesterol and triglycerides decreased slightly

Albumin to creatinine ratio declined by 17%

C-reactive protein decreased by 22%

Quality-of -life scores improved

Adverse effects of exenatide over 26 weeks. Nausea 23%; diarrhea 18%; vomiting 11% fatigue 6%; and constipation 6%; 11 patients withdrew because of adverse effects. There were no episodes of major hypoglycemia; two events of minor hypoglycemia.

Some patients developed antibodies to exenatide. The investigators found no adverse effects from this.

DISCUSSION

1. Once-weekly injections of exenatide over 26 weeks, on a background of metformin, elicited significantly greater improvement in HbA1c than maximum doses of either sitagliptin or pioglitazone.
2. “These data suggest that exenatide once weekly offers clinically meaningful improvements in patients not achieving adequate glycemic control on metformin alone.”
3. The 3 drugs have shown sustained improvements in glycemic control over 2 years.

4. To achieve optimum treatment of DM-2, weight and intermediates such as lipids and BP should be considered. Exenatide was associated with greater weight loss than either sitagliptin or pioglitazone.
5. Improvements in lipids and markers of cardiovascular risk were noted to varying degrees in all 3 treatments. Exenatide was the only drug associated with favorable mean changes in all the parameters.
6. Consistent with the reduction in systolic BP, exenatide significantly reduced the albumen/creatinine ratio.
7. Further studies are required to establish whether these reductions in risk factors will translate into reduction in CVD outcomes.
8. “Adverse events were generally mild to moderate.”
9. All 3 drugs, on a background of metformin, were associated with a low frequency of hypoglycemia.
10. The adverse GI events of exenatide should be taken into account when assessing exenatide as a potential treatment.
11. The improvements in HbA1c and bodyweight with once-weekly exenatide, suggest that the drug should be considered as an adjunct to metformin in patients needing improvements in glucose control and bodyweight, and in whom hypoglycemia needs to be kept to a minimum.

CONCLUSION

Addition of exenatide once weekly to metformin achieved the goal of better glycemic control with weight loss and minimum hypoglycemia more often than did the addition of maximum doses of sitagliptin or pioglitazone.

Lancet August 2, 20110; 376:431-39 original investigation ,by DURATION-2 Study Group (Diabetes therapy Utilizing Researching changes in A1c, weight and other factors Trough Intervention with exenatide, ONce weekly) first author Richard M Bergenstal, International Diabetes center at Park Nicollet, Minneapolis, Minn. Funded by Amylin Pharmaceuticals and Lilly

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